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37 C.F.R. 1.8

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Vladimir L. Makarov
John P. Langmore

Serial No.: 09/801,346

Filed: March 6, 2001

For: COMPOSITIONS AND METHODS FOR
ANALYSIS OF NUCLEIC ACIDS

Group Art Unit: 1631

Examiner: Unknown

Atty. Dkt. No.: UMIC:039USC1/DLP

RESPONSE TO NOTICE OF INCOMPLETE REPLY
DATED JULY 10, 2001

Commissioner for Patents
Washington, D.C. 20231

Commissioner:

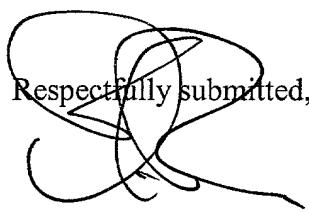
In response to the Notice of Incomplete Reply mailed July 10, 2001, Applicants hereby provide substitute drawings in compliance with 37 CFR 1.84. These are the same drawing that have been accepted and published in the parent application, now U.S. Patent 6,197,557. A copy of the Notice of Incomplete Reply is also enclosed.

Pursuant to 37 C.F.R. § 1.136(a), for an extension of time of one month to and including August 10, 2001 in which to respond to the Notice of Incomplete Reply dated July 10, 2001.

Pursuant to 37 C.F.R. § 1.17, a check in the amount of \$55.00 is enclosed as the process fee for a one-month extension of time.

If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski L.L.P. Account No.: 50-1212/10101172/DP01982.

Respectfully submitted,


David L. Parker
Reg. No. 32,165
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512/ 536-3055

Date: August 3, 2001

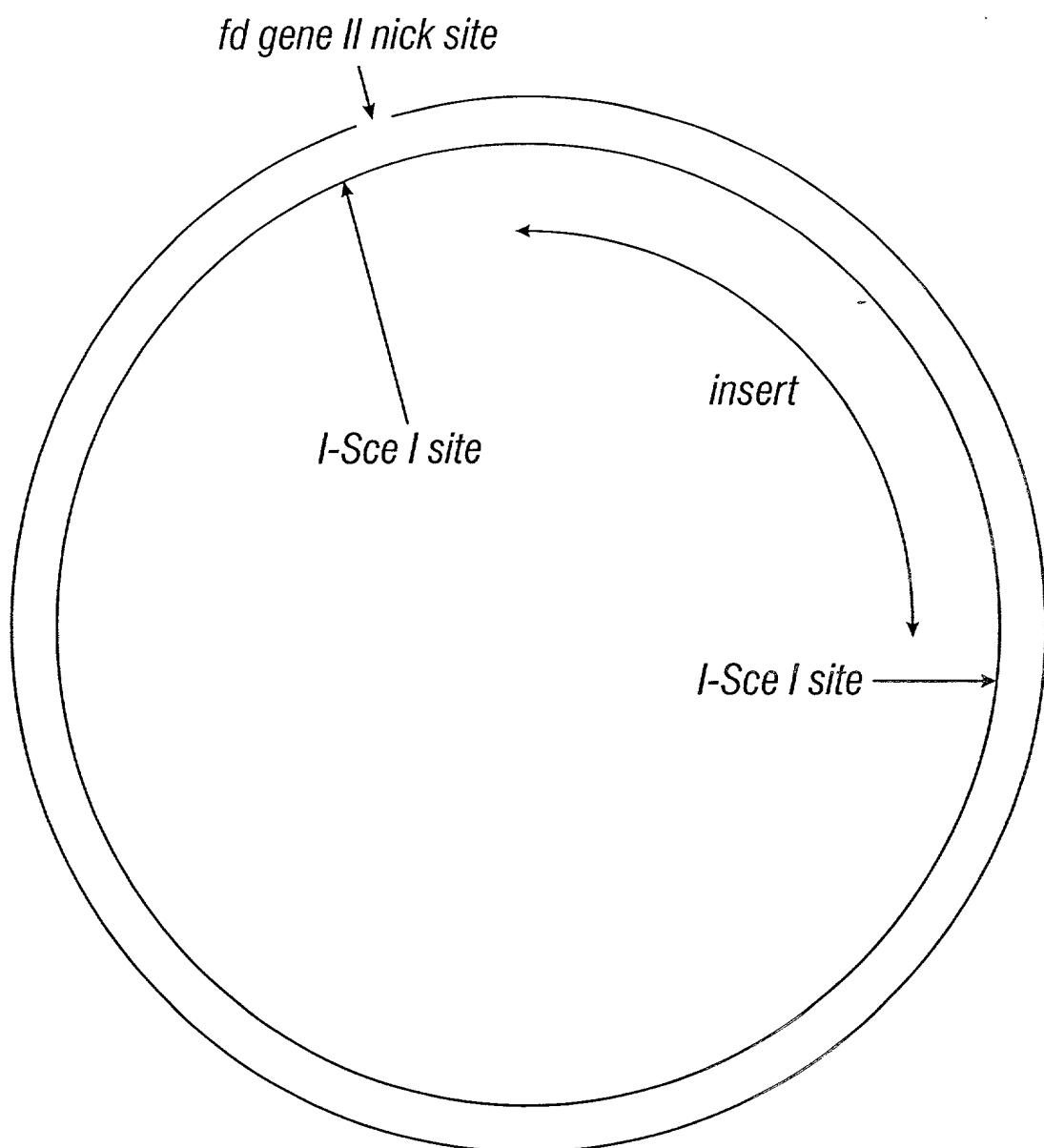


FIG. 1

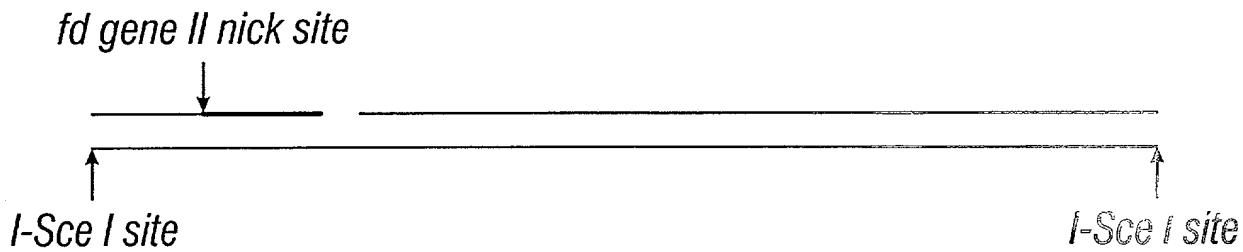


FIG. 2

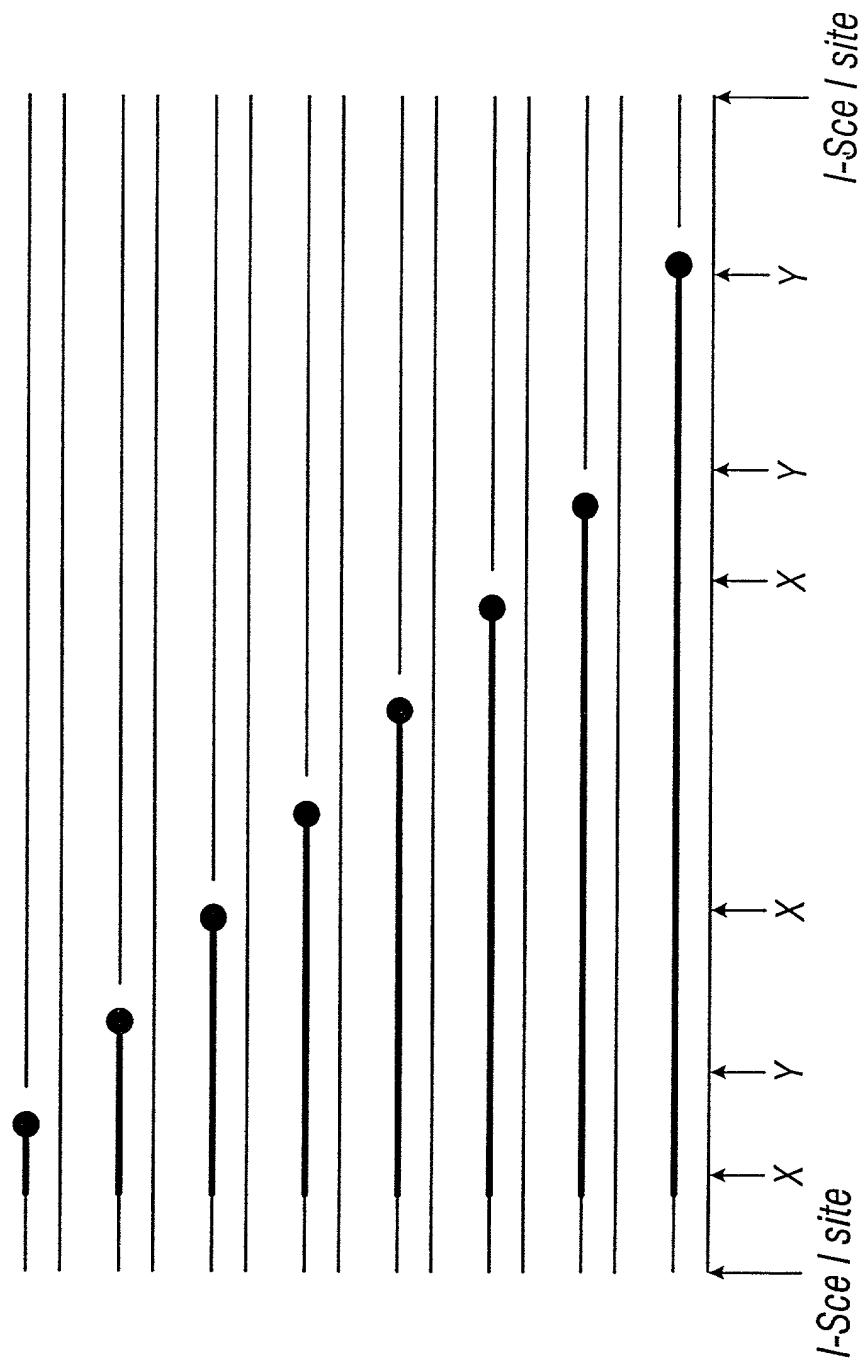


FIG. 3

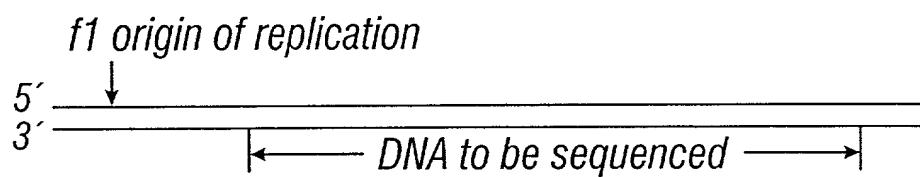


FIG. 4A



FIG. 4B



FIG. 4C



FIG. 4D



FIG. 4E

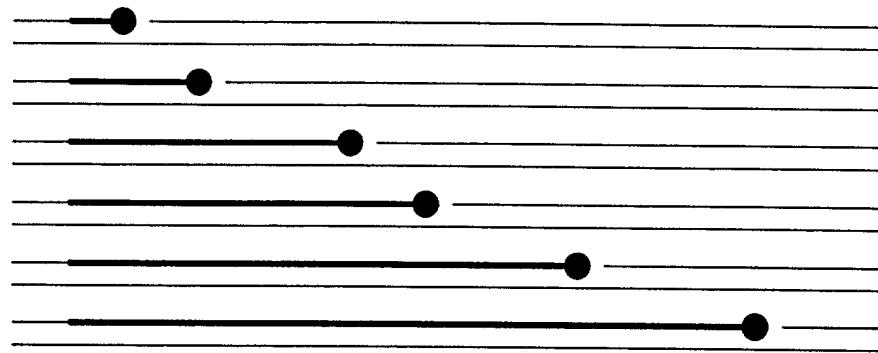


FIG. 4F

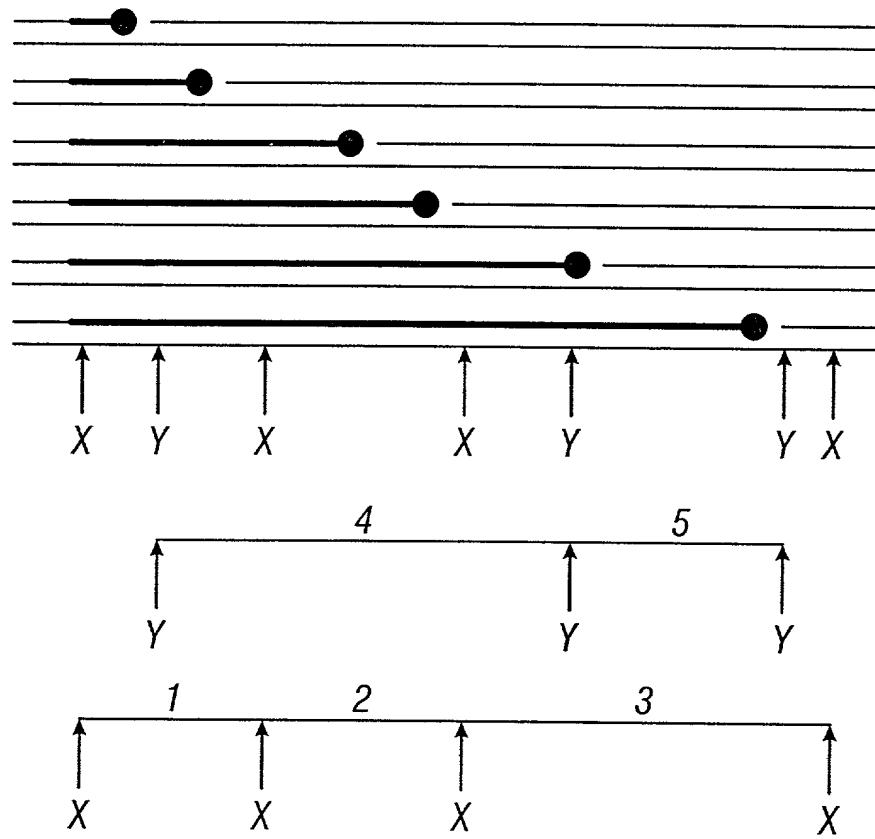


FIG. 4G

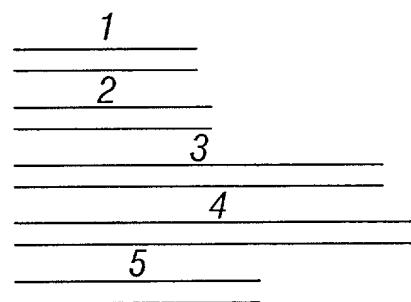


FIG. 4H

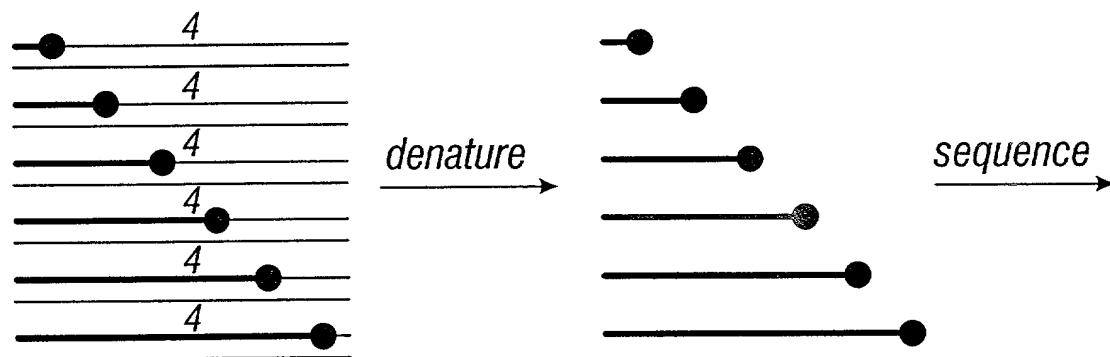
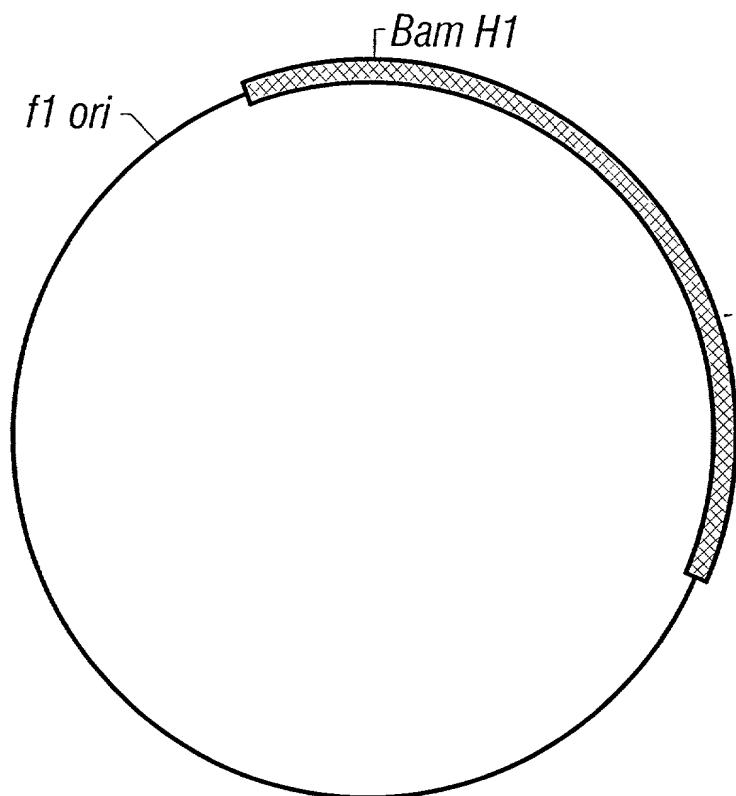


FIG. 4I



*Restriction with Bam H1
to linearize SRR products*

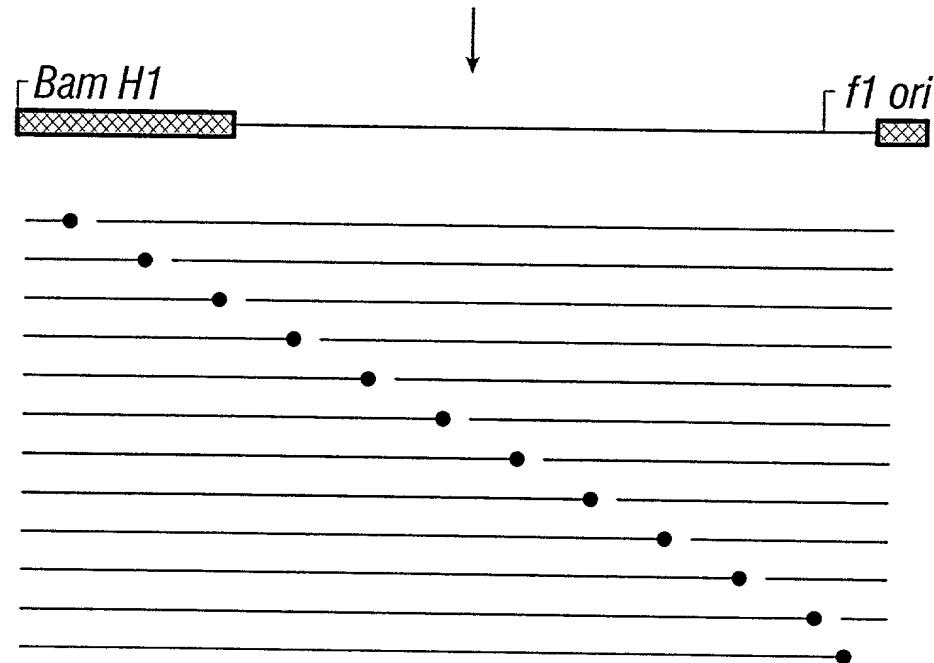


FIG. 5

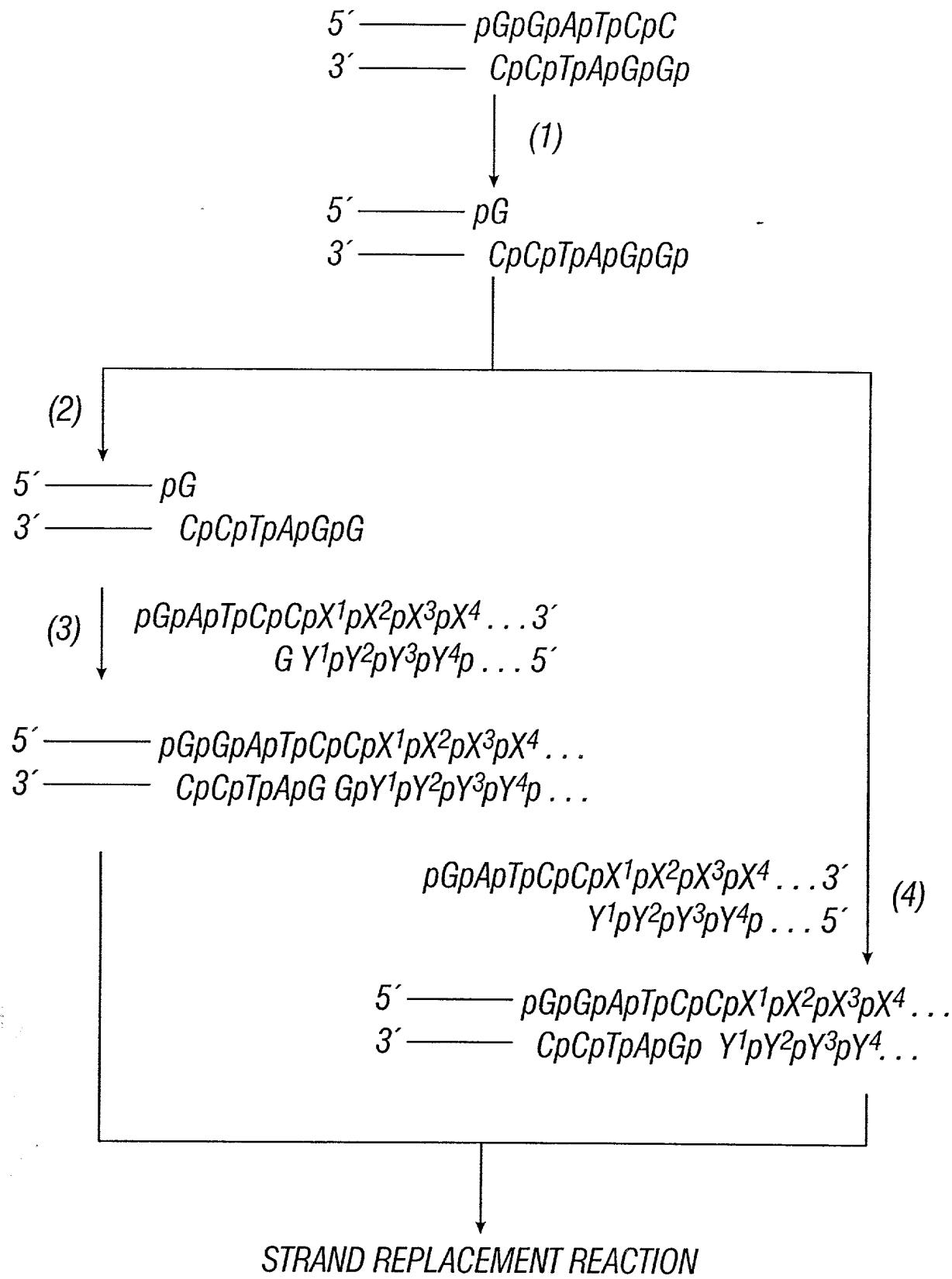


FIG. 6

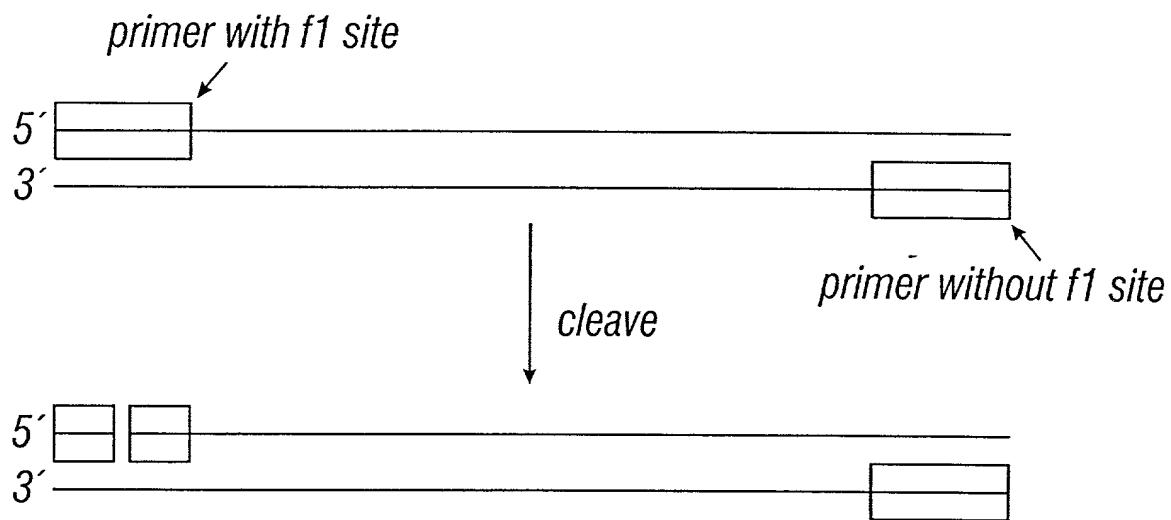


FIG. 7A

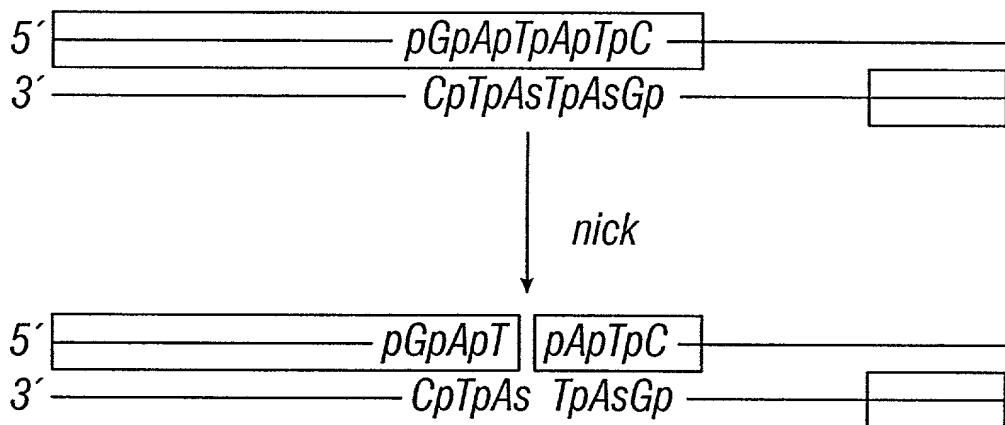


FIG. 7B

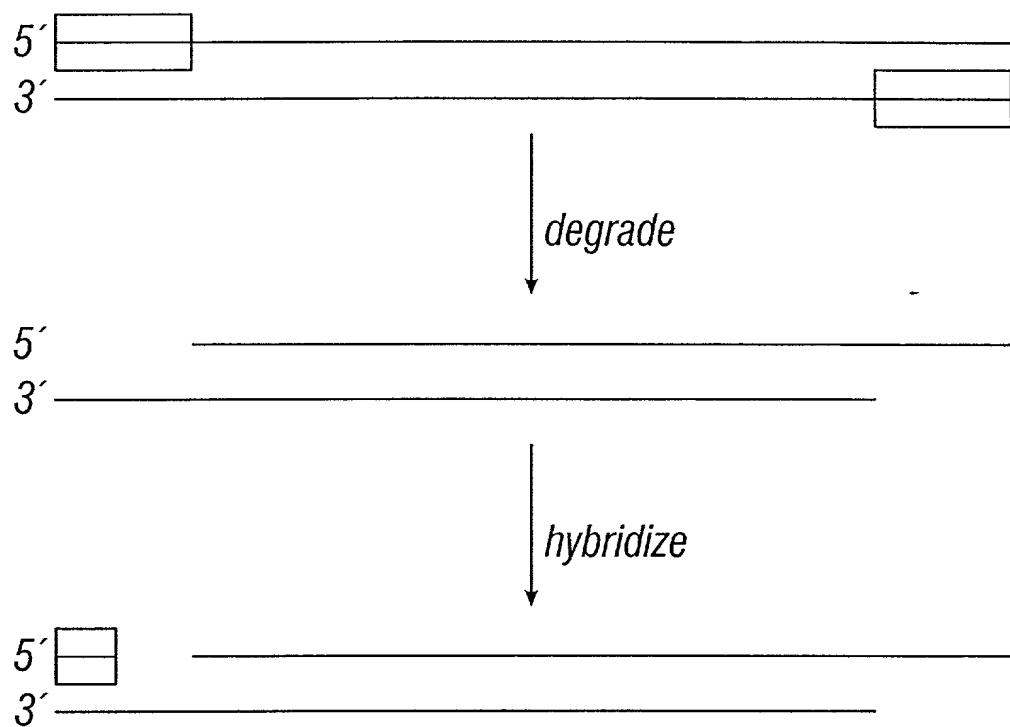


FIG. 7C

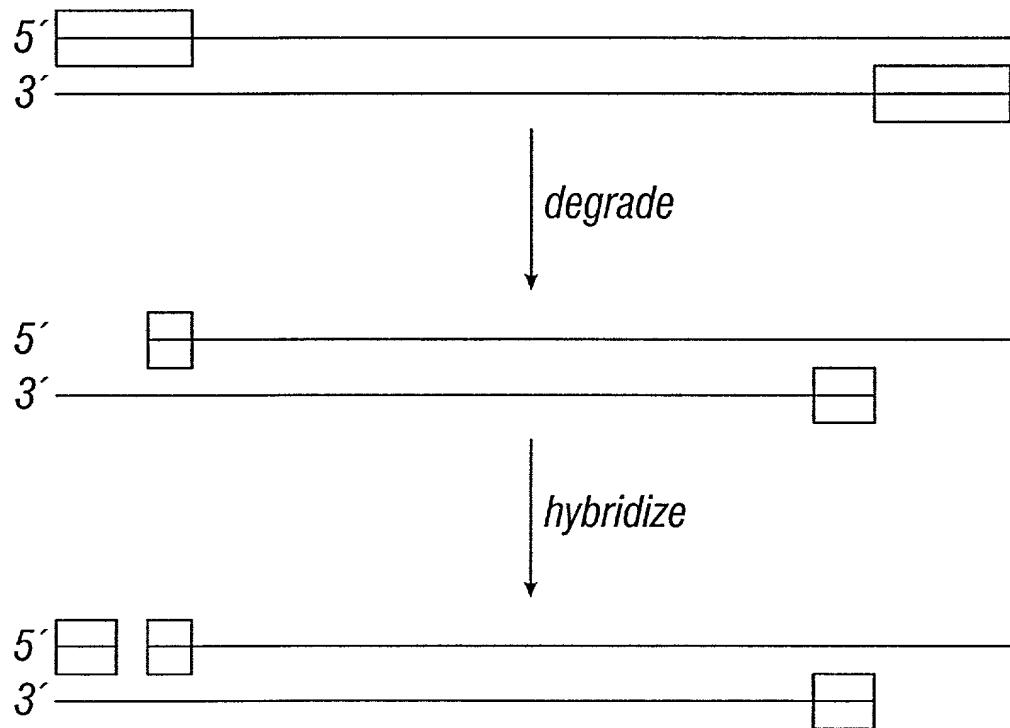


FIG. 7D

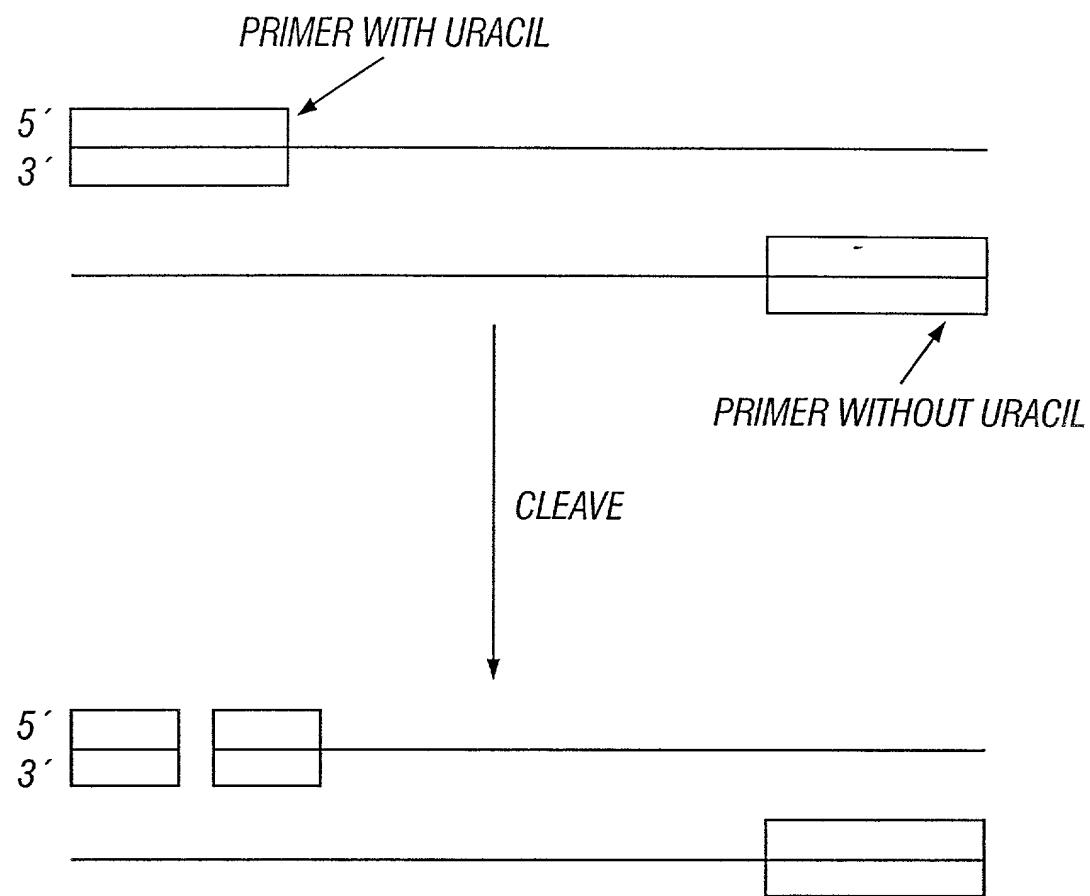


FIG. 7E

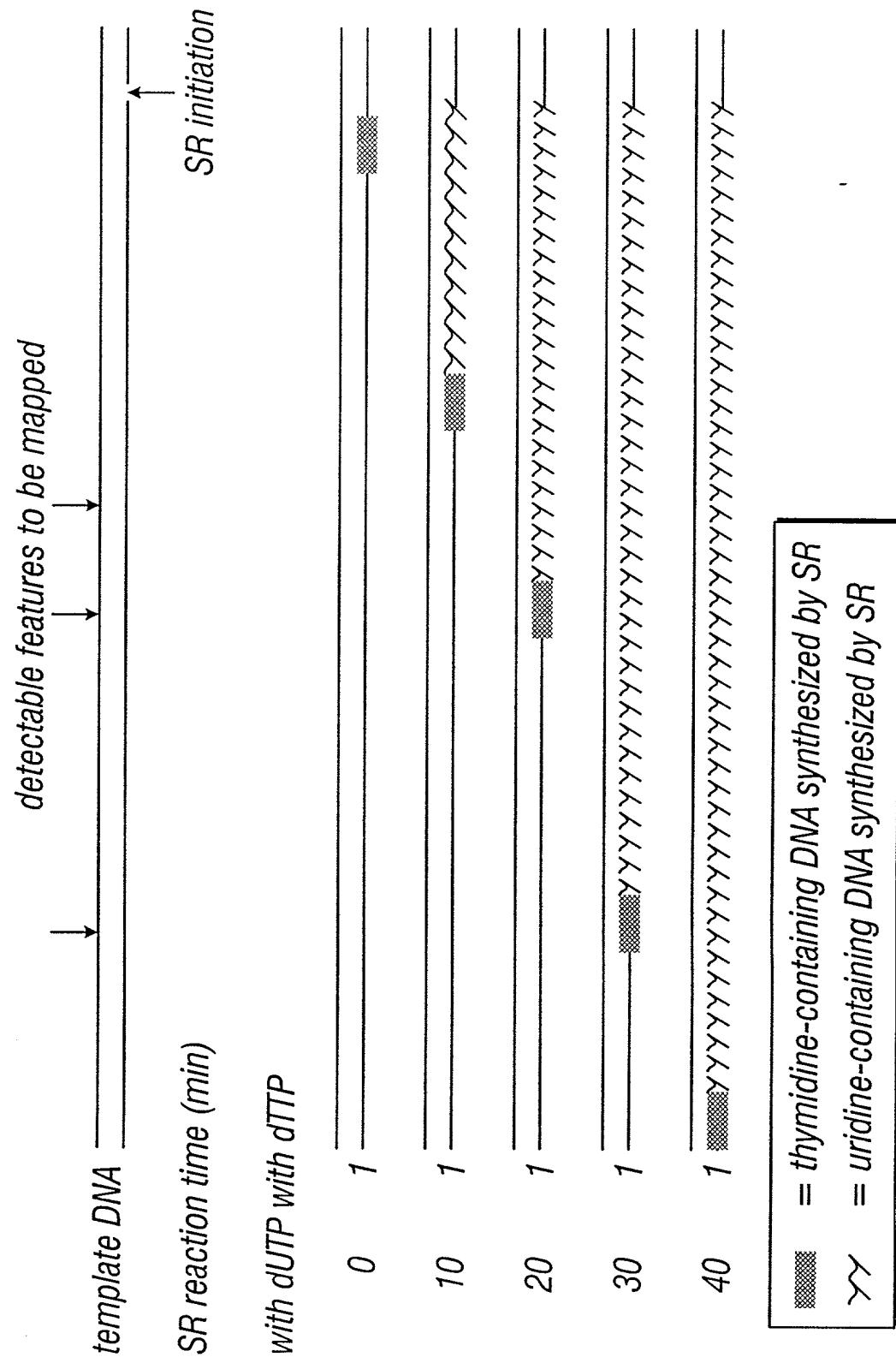


FIG. 8

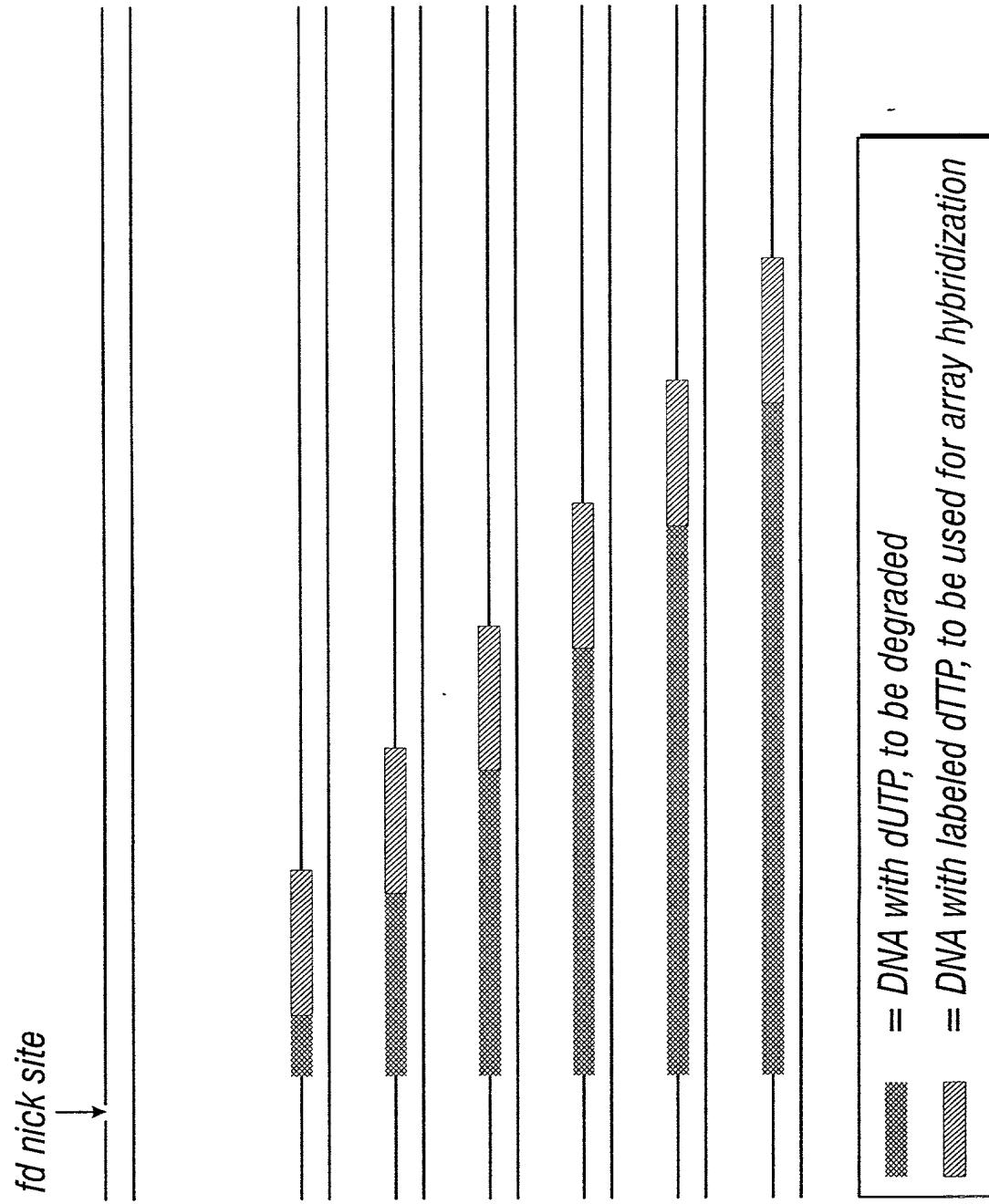
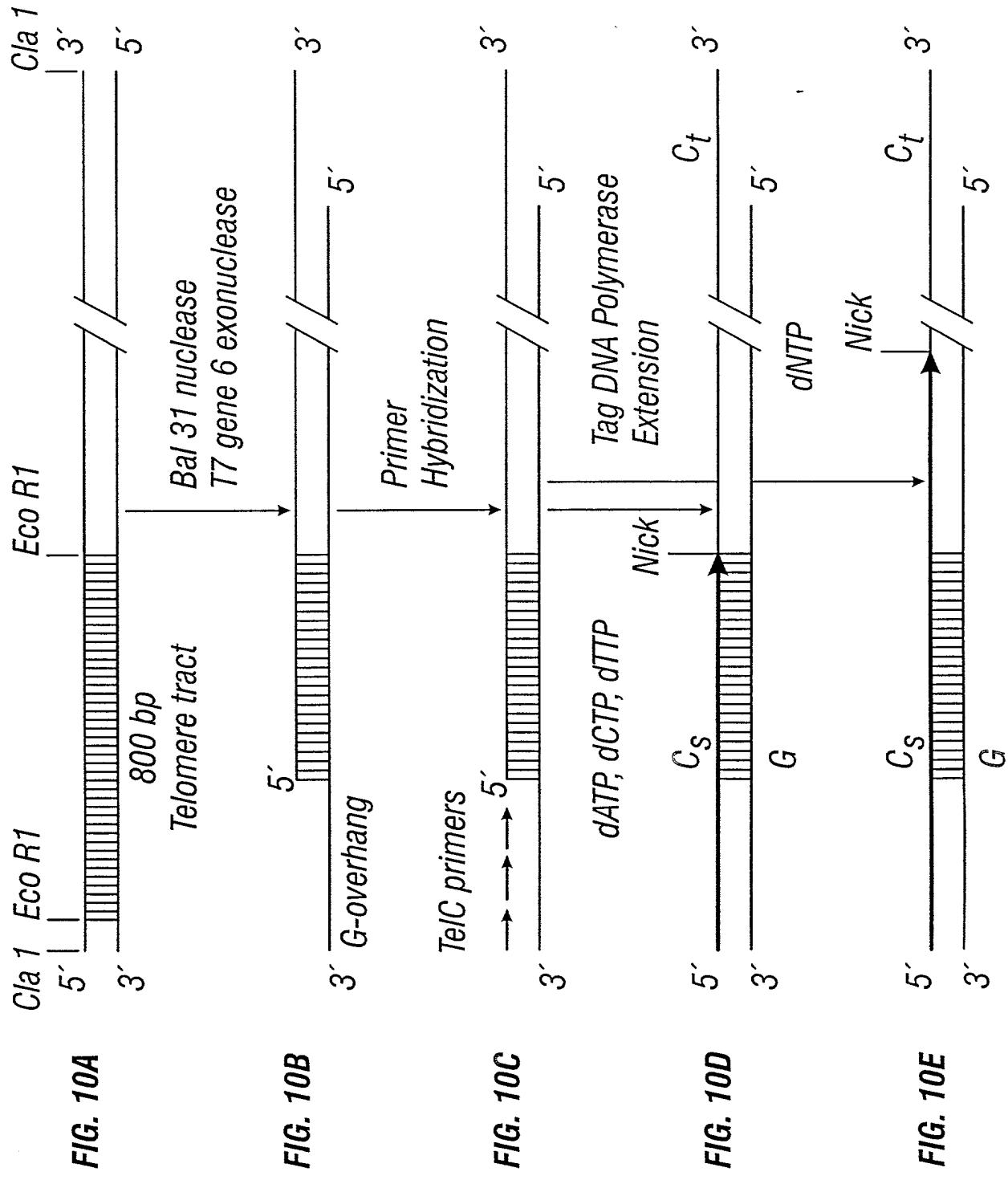


FIG. 9



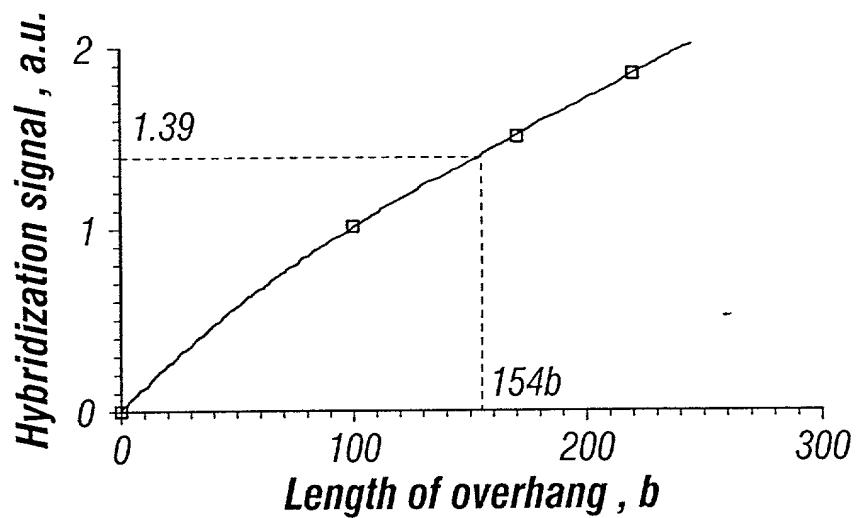
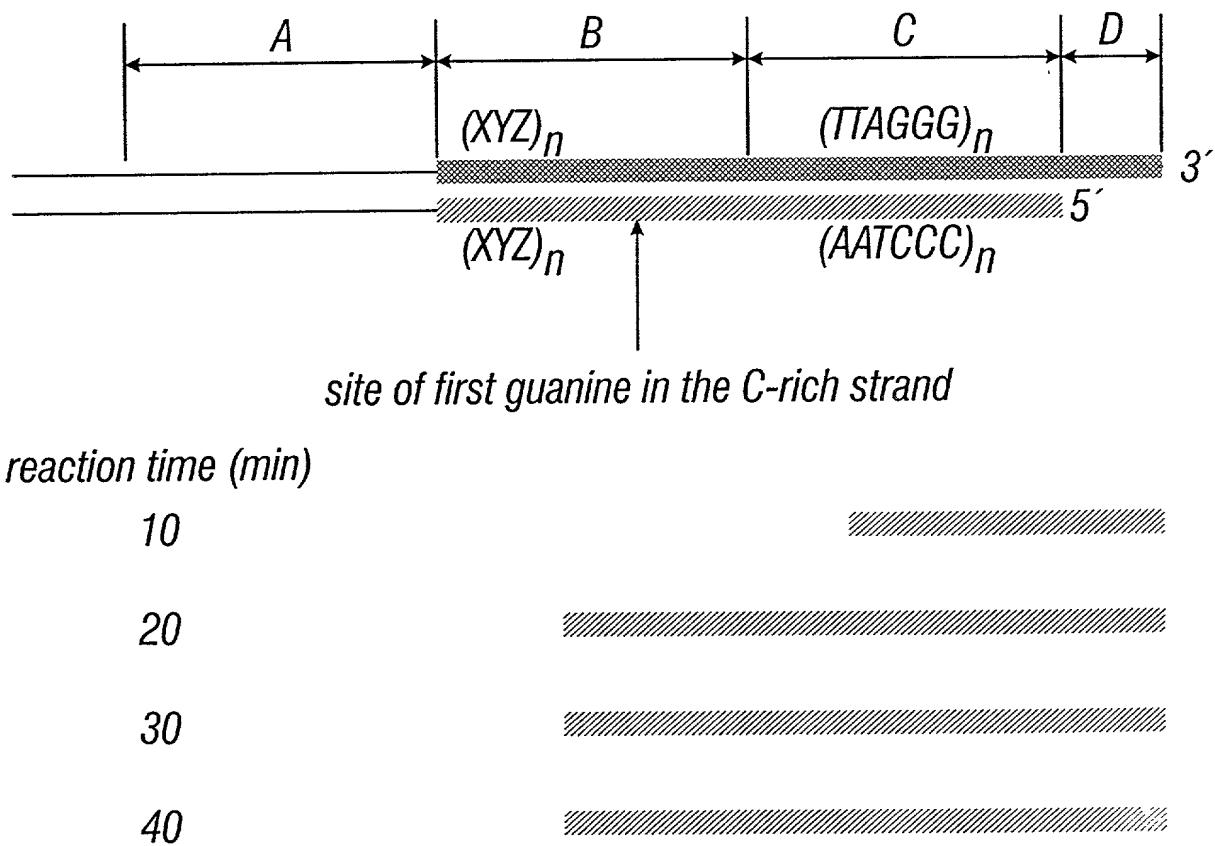
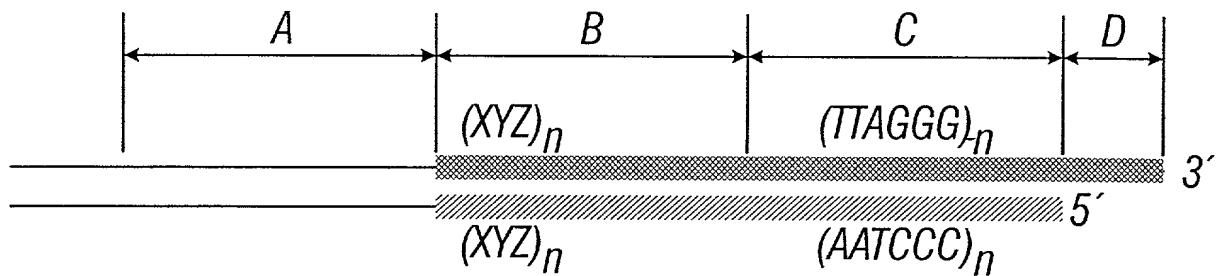


FIG. 11



■ =DNA synthesized by SR using only dATP, dTTP, and dCTP

FIG. 12



reaction time (min)

with dUTP with dTTP

■ =thymidine-containing DNA synthesized by PENT

yyy =uridine-containing DNA synthesized by PENT

FIG. 13

B
1 2 3 4 5 6 7 8 9

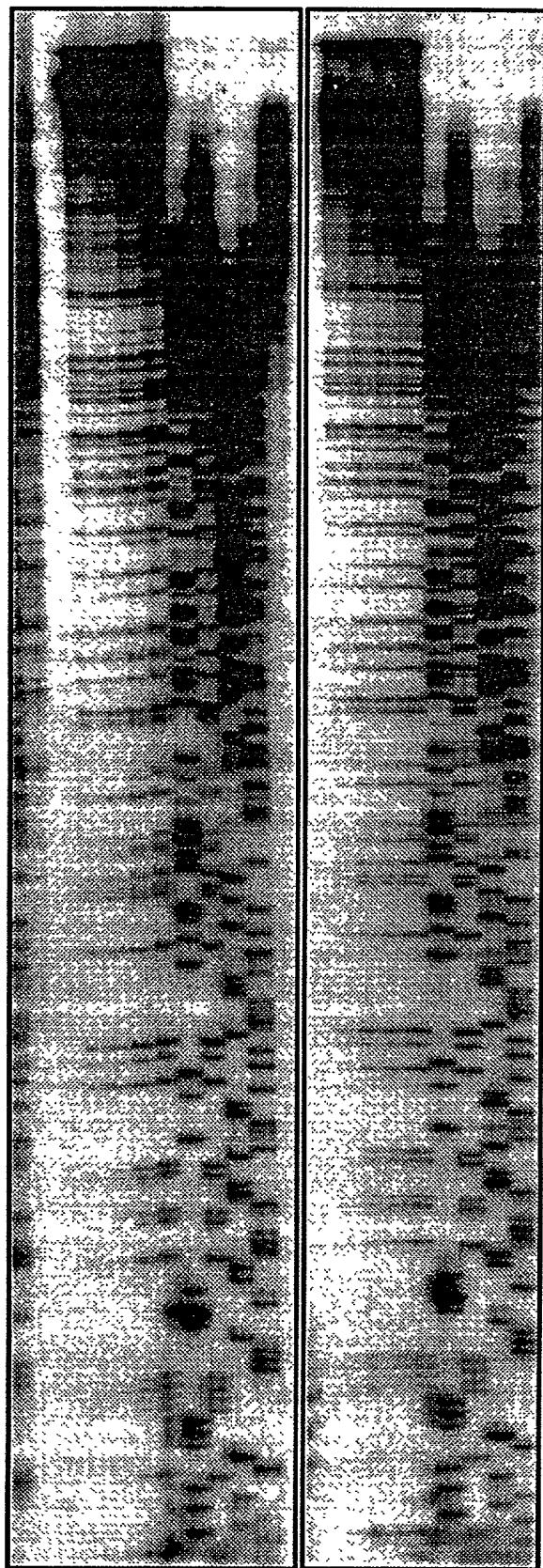


FIG. 14B

A
1 2 3 4 5 6 7 8 9

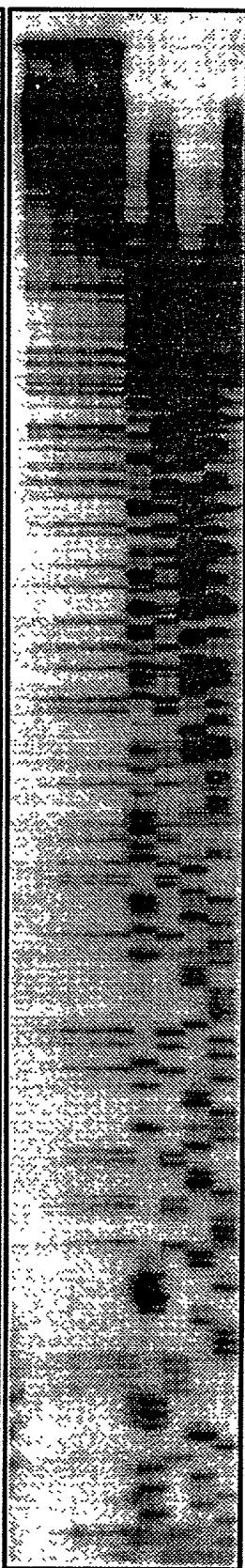


FIG. 14A

5' O---T-A-C-T-A-T-G-G-T-T-A---3'
 3' ---A-T-G-A-T-A-C-C-A-A-T---5'
 1 2 3 4 5 6 7 8 9101112

PRIMER X UNKNOWN DNA SEQUENCE PRIMER Y

→

O-----A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T- C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A- T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C- A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T- T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A- G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----

PCR-AMPLIFIED WITH DETECTION TAG AT 5' END OF
 PRIMER X. NUMBERS LABEL THE 12 UNKNOWN BASES.

RANDOM DEGRADATION (ONLY DAMAGED UPPER STRAND SHOWN)

O-----T-A-C-T-A-T- 15A
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T-A-T-G-G-T- 15B
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T-A-T-G-G-T-
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----

FIG. 15

EXPOSE 3' OH AT DAMAGE SITES

O-----A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T- C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A- T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C- A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T- T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T-A-T-G-G-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----

FIG. 15A

INCORPORATE BIOTINYLATED DDTTP AT POSITIONS
OPPOSITE ADENINE IN TEMPOLATE STRAND

IMMOBILIZE BIOTINYLATED STRANDS AND REMOVE
NON-BIOTINYLATED STRANDS

O-----T-A-C-T-A-T-G-G-T.
O-----T-A-C-T-A-T-G-G-T-T.
O-----T-A-C-T-A-T-G-G-T-T-T.

RELEASE BIOTINYLATED STRANDS, SEPARATE BY ELECTROPHORESIS, AND DETECT TAGGED PRIMERS (DARK BARS REPRESENT POSITIONS OF THYMINE)

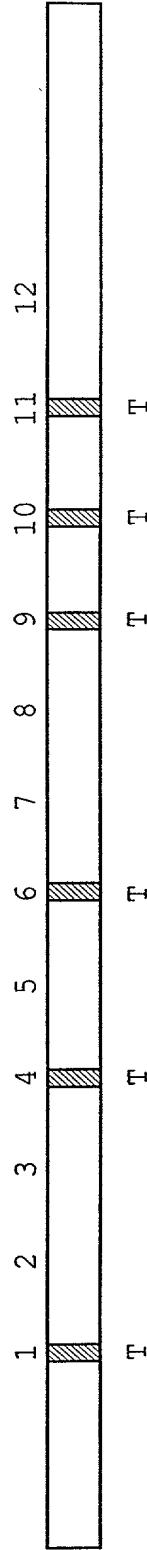


FIG. 15B

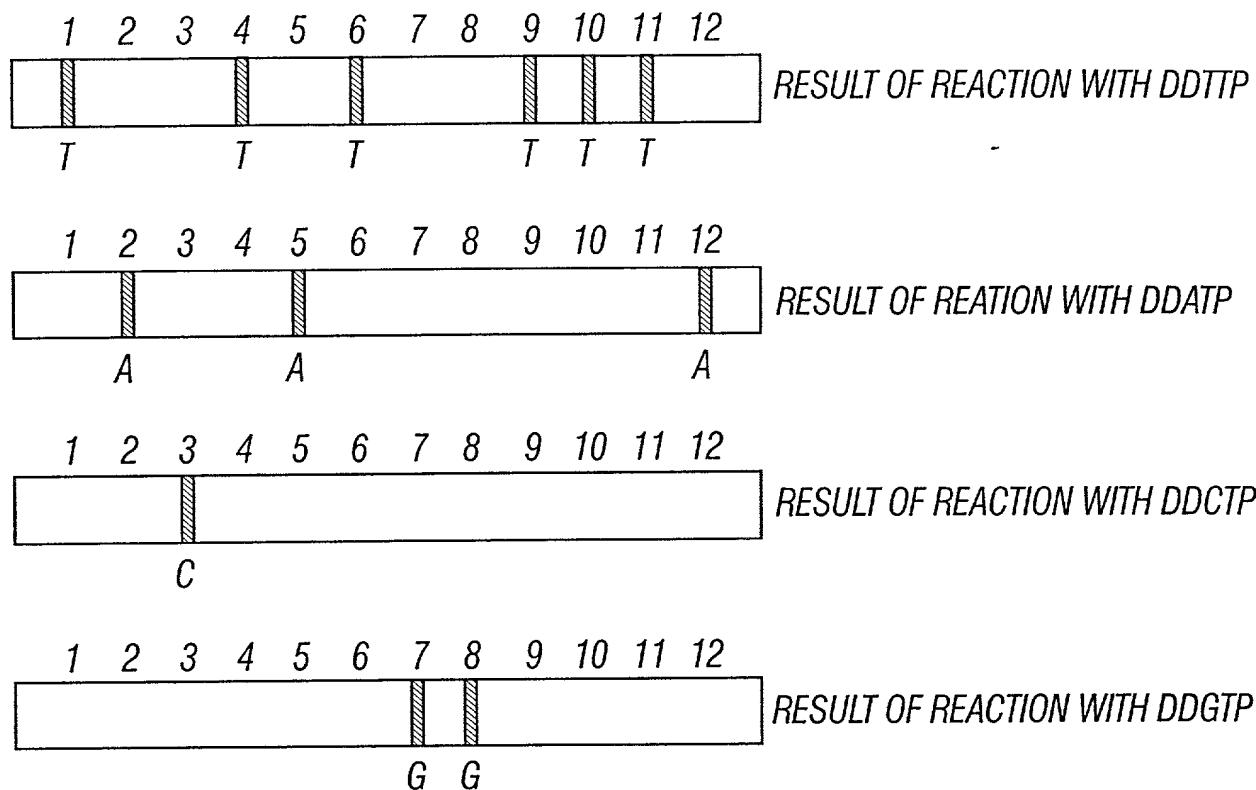


FIG. 16A

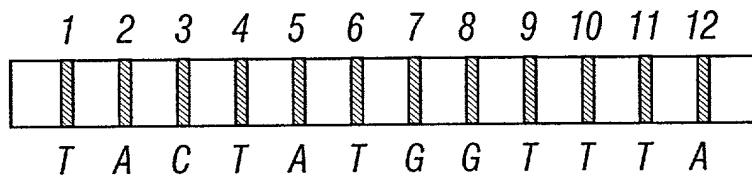


FIG. 16B

5' O-----T-A-C-T-A-T-G-G-T-T-T-A-----3'
 3' -----A-T-G-A-T-A-C-C-A-A-T-----5'

1 2 3 4 5 6 7 8 9101112
 PRIMER X UNKNOWN DNA SEQUENCE PRIMER Y

PCR-AMPLIFIED WITH DETECTION TAG AT 5' END OF
 PRIMER X. NUMBERS LABEL THE 12 UNKNOWN BASES.

RANDOM DEGRADATION (ONLY DAMAGED UPPER STRAND SHOWN)

O-----A-C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T- C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A- T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A-C-T- T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A-C-T-A- G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A-C-T-A- -----A-T-G-A-T-A-C-C-A-A-A-T-----

EXPOSE 3' OH AT DAMAGE SITES

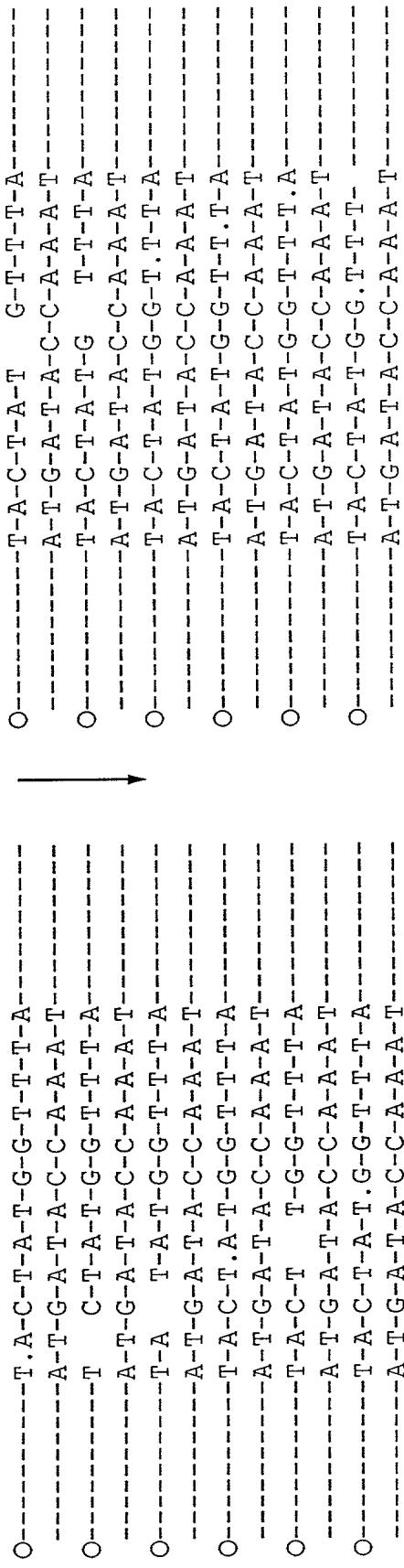
O-----A-C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T- C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A- T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 O-----T-A-C-T- T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A-C-T-A- G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 O-----T-A-C-T-A- -----A-T-G-A-T-A-C-C-A-A-A-T-----

17A
 17B

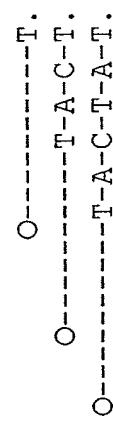
FIG. 17A

FIG. 17

incorporate biotinylated ddTTP at positions opposite adenine in template strand



immobilize biotinylated strands and remove non-biotinylated strands



release biotinylated strands, separate by electrophoresis, and detect tagged primers (dark bars represent positions of terminal thymine)

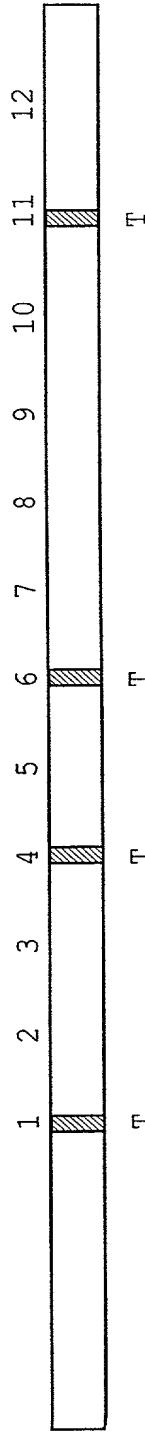


FIG. 17B

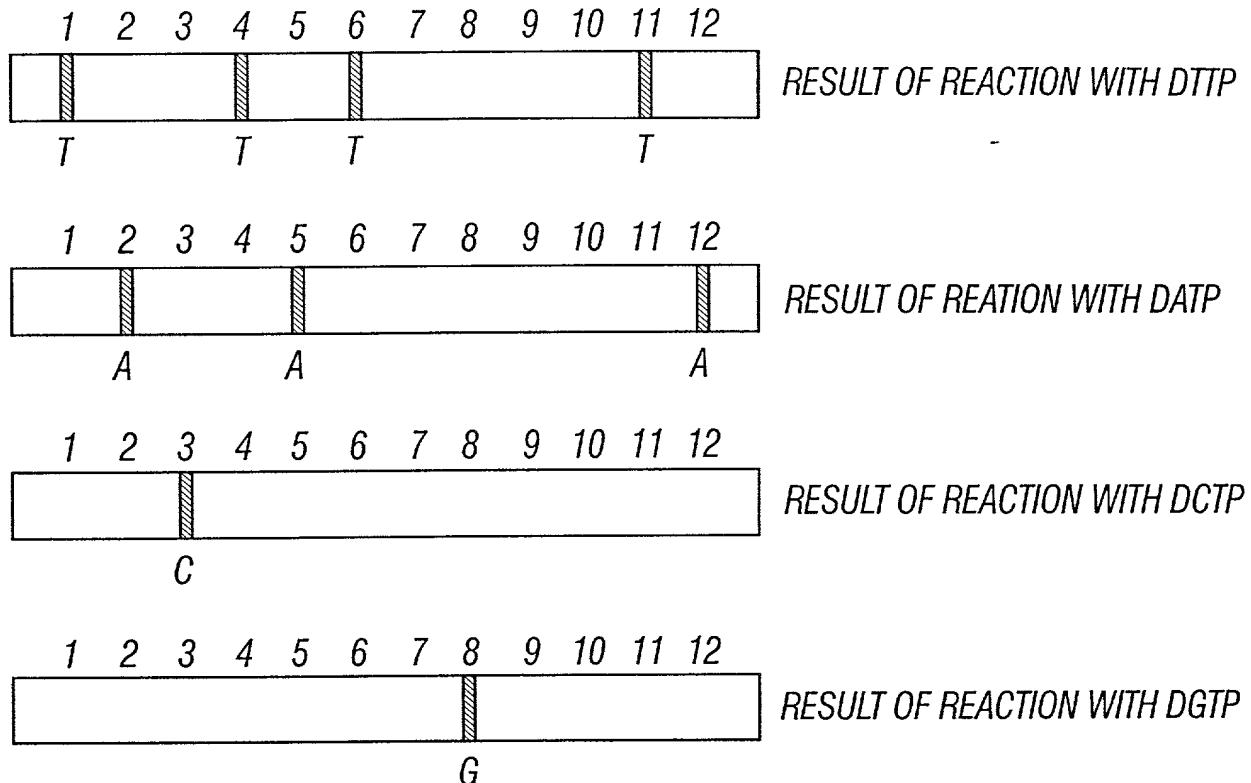


FIG. 18A

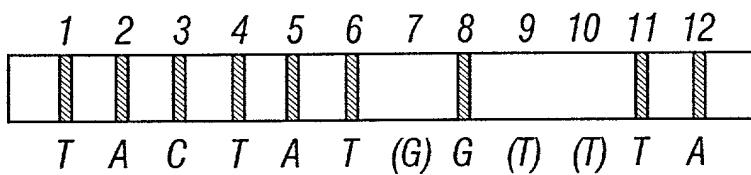


FIG. 18B

5' O-----T-A-C-T-A-T-G-G-T-T-T-A-----3'
 3' -----A-T-G-A-T-A-C-C-A-A-T-----5'
 1 2 3 4 5 6 7 8 9101112

PRIMER X UNKNOWN DNA SEQUENCE PRIMER Y

-----A-C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T- C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A- T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T- T-A-C-T-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T- T-A-C-T-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----

PCR-AMPLIFIED IMMobilized AT 5' END OF PRIMER
 X. NUMBERS LABEL THE 12 UNKNOWN BASES.

RANDOM DEGRADATION (ONLY DAMAGED UPPER STRAND SHOWN)

-----T-A-C-T-A-T- G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T-A-T-G- T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-T-----
 -----T-A-C-T-A-T-G-G-G- G-G-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T- T-A-C-T-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----

EXPOSE 3'OH AT DAMAGE SITES

-----A-C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-T-----
 -----T- C-T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 -----T-A- T-A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-A-T-----
 -----T-A-C- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-T-----

19A

19B

-----A-T-G-A-T-A-C-C-C-A-A-T-----
 -----A-T-G-A-T-A-C-C-C-A-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-A-T-----
 -----T-A-C-T- A-T-G-G-T-T-T-A-----
 -----A-T-G-A-T-A-C-C-C-A-A-T-----

FIG. 19A

FIG. 19

INCORPORATE TAGGED DDTTP AT POSITIONS
OPPOSITE ADENINE IN TEMPLATE STRAND

O-----T.A-C-T-A-T-G-G-T-T-T-A-----
O-----A-T-G-A-T-A-C-C-A-A-A-T-----
O-----C-T-A-T-G-G-T-T-T-A-----
O-----A-T-G-A-T-A-C-C-A-A-A-T-----
O-----T-A-T-G-G-T-T-T-A-----
O-----A-T-G-A-T-A-C-C-A-A-A-T-----
O-----T-A-C-T-A-T-G-G-T-T-T-A-----
O-----A-T-G-A-T-A-C-C-A-A-A-T-----
O-----T-A-C-T-T-G-G-T-T-T-A-----
O-----A-T-G-A-T-A-C-C-A-A-A-T-----
O-----T-A-C-T-A-C-C-A-A-A-T-----

C-----T-A-C-T-A-T G-T-T-T-A-----
-----A-T-G-A-T-A-C-C-A-A-T-----
O-----T-A-C-T-A-T-G T-T-T-A-----
-----A-T-G-A-T-A-C-C-A-A-T-----
O-----T-A-C-T-A-T-G-G-T. T-T-A-----
-----A-T-G-A-T-A-C-C-A-A-T-----
O-----T-A-C-T-A-T-G-G-T-T. T-A-----
-----A-T-G-A-T-A-C-C-A-A-T-----
O-----T-A-C-T-A-T-G-G-T-T-T. A-----
-----A-T-G-A-T-A-C-C-A-A-T-----
O-----T-A-C-T-A-T-G-G-T-T-T-----
-----A-T-G-A-T-A-C-C-A-A-T-----

DENATURE AND WASH TO REMOVE ALL STRANDS THAT ARE
NOT TAGGED AT 5' END

MOBILIZE STRANDS, SEPARATE BY
ELECTROPHORESIS, AND DETECT 'TAGGED' BASES
(DARK BARS REPRESENT POSITIONS OF THYMINE)

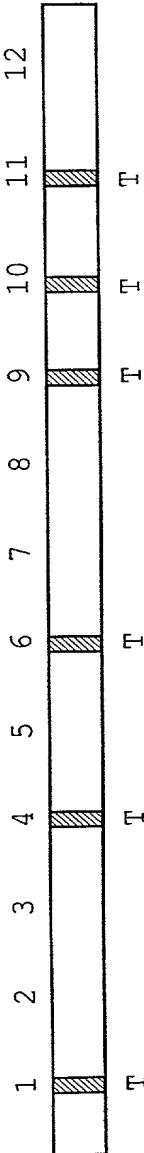


FIG. 19B

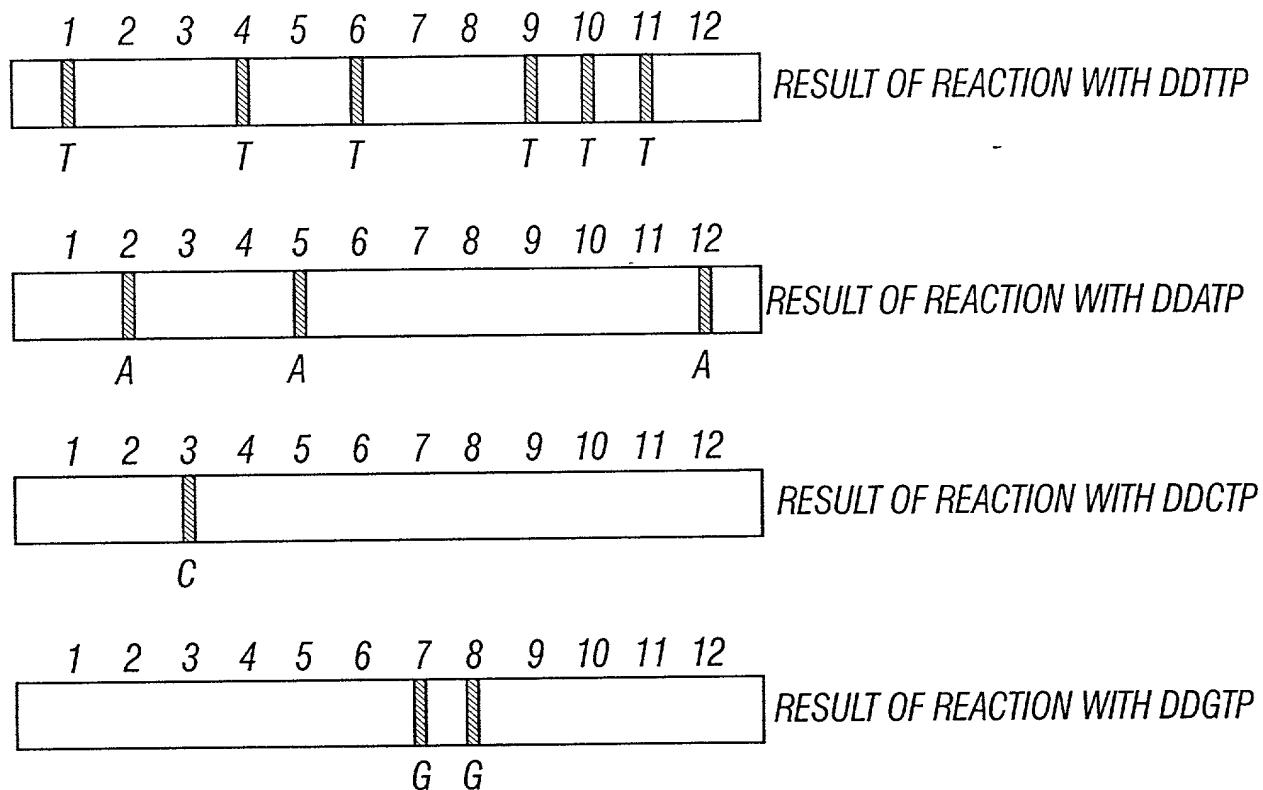


FIG. 20A

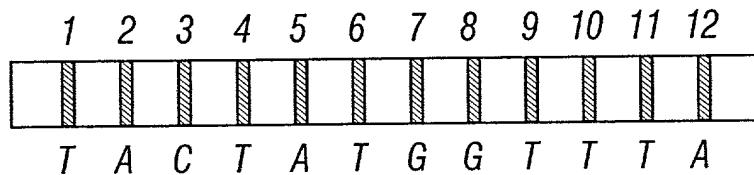
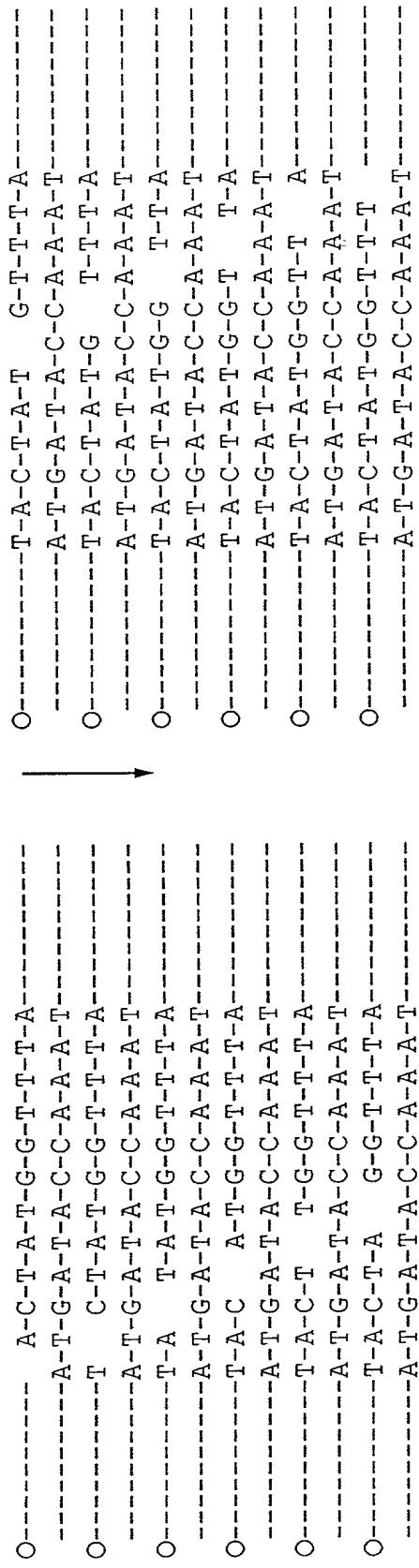
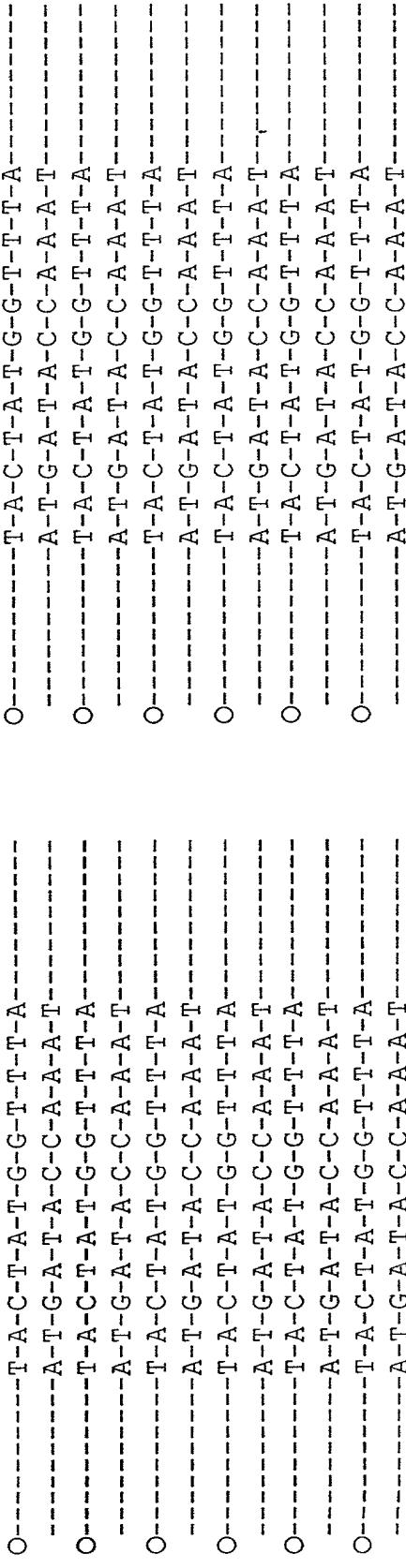


FIG. 20B

PCR amplify, immobilize, and expose
at random sites as in Fig. 5.



Block ends opposite T, G' & C with ddATP, ddGTP, ddCTP
(shown in bold letters), remove ddNTPs, then add dTTP.



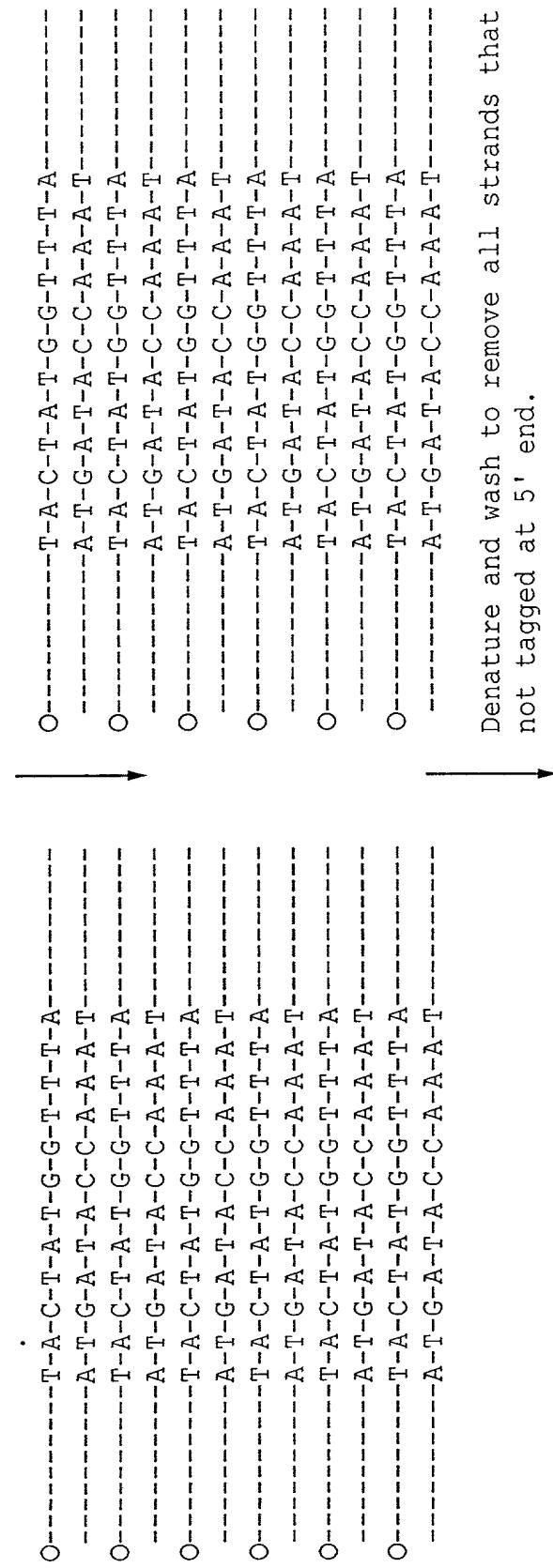
21A	21B
-----	-----

FIG. 21

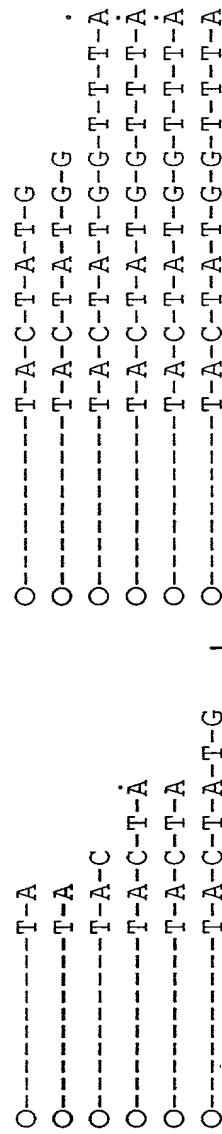
FIG. 21A

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Block ends opposite A, G & C with ddTTP, ddGTP, ddCTP (shown in bold letters), remove ddNTPs, then add tagged ddATP.



Denature and wash to remove all strands that are not tagged at 5' end.



Mobilize strands, separate by electrophoresis, and detect taqged bases (dark bars).

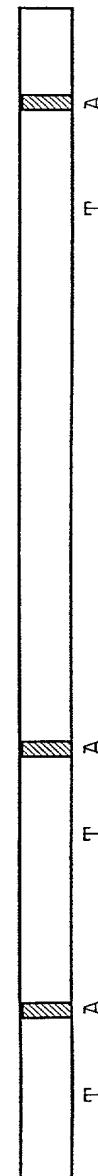


FIG. 21B

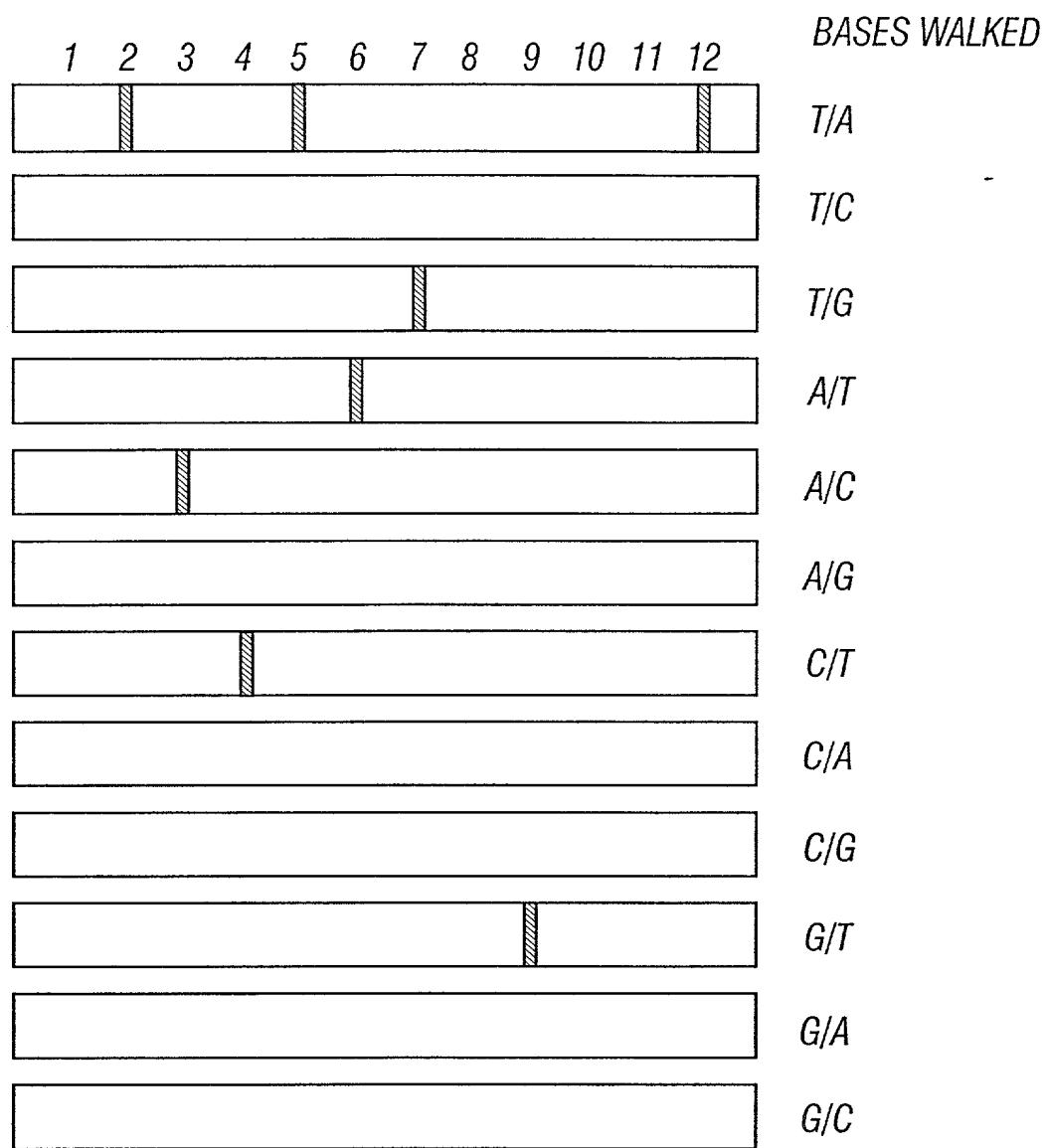


FIG. 22A

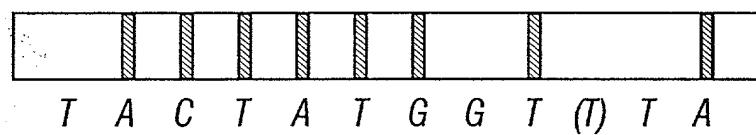
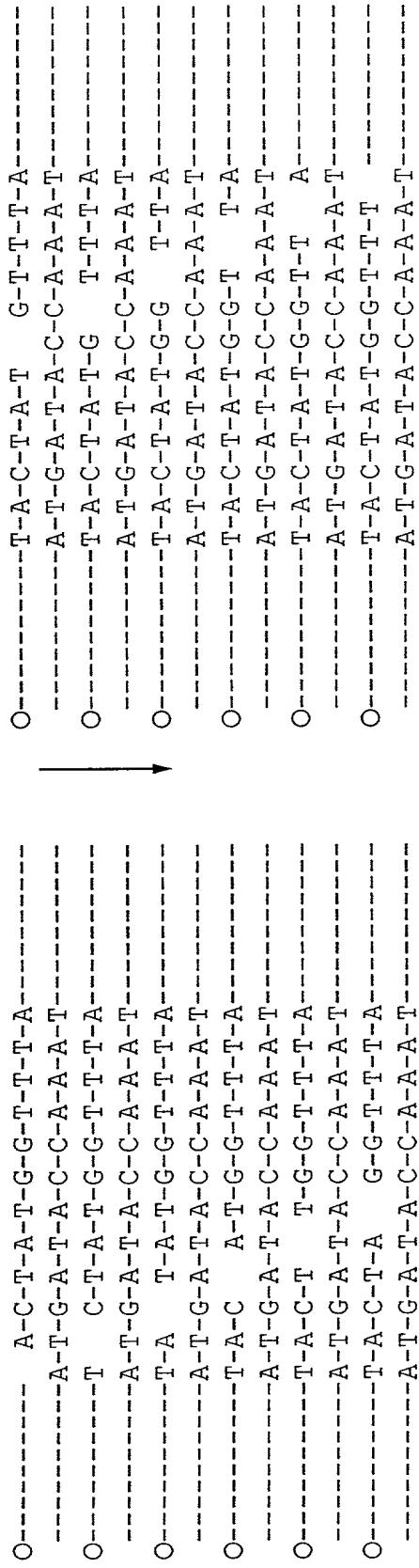
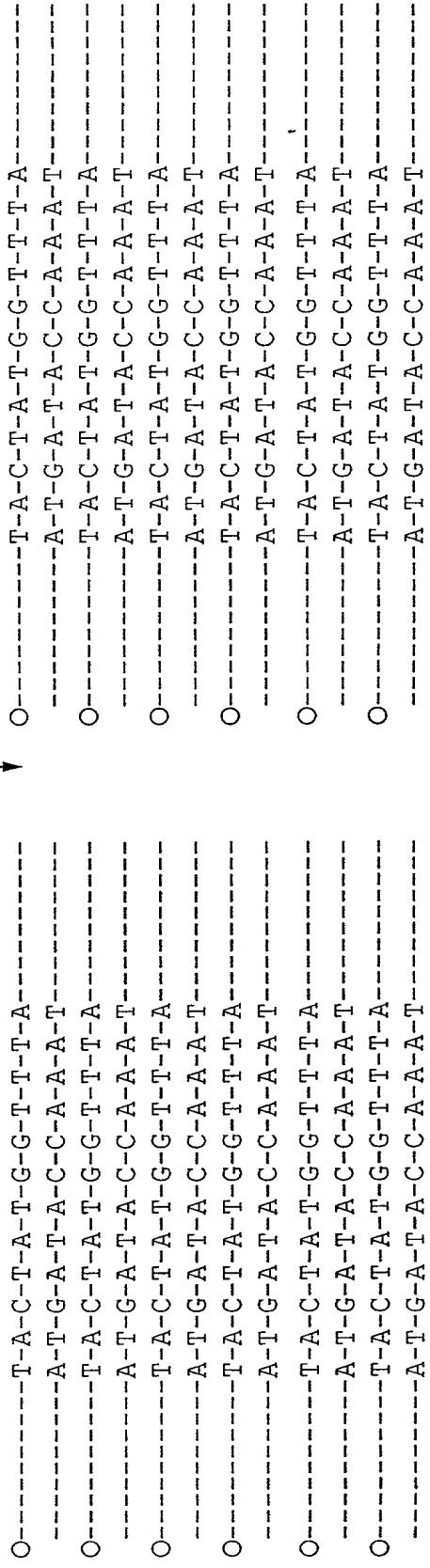


FIG. 22B

PCR amplify, immobilize, and expose 3' OH at random sites as in Fig. 5.



Block ends opposite T, G & C with ddATP, ddGTP, ddCTP (shown in bold letters), remove ddNTPs, then add dTTP.



23A	23B
-----	-----

FIG. 23

FIG. 23A

Block ends opposite A, G & C with ddTTP, ddGTP, ddCTP (shown in bold), remove ddNTPs, then add dATP.

Block ends opposite **A**, **G** & **C** with **ddTTP**, **ddGTP**, **ddCTP**
 Block ends opposite **T**, **G** & **C** with **ddATP**, **ddGTP**, **ddCTP**
 (shown in bold), remove **ddNTPs**, then add tagged **ddTTP**.

Remove all non-immobilized DNA, then release, size-separate, and detect strands with tagged terminal T.

A horizontal number line with tick marks labeled from 1 to 12. A small square is shaded at the tick mark for 1.

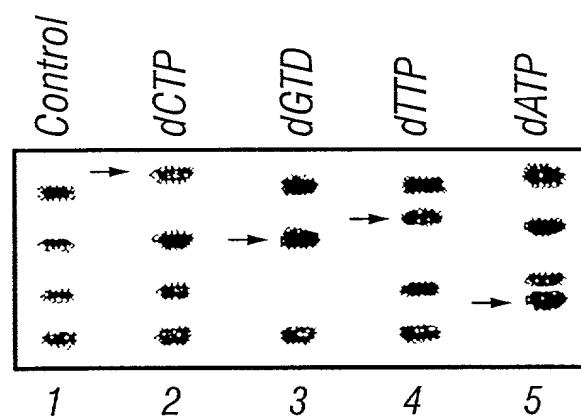


FIG. 24

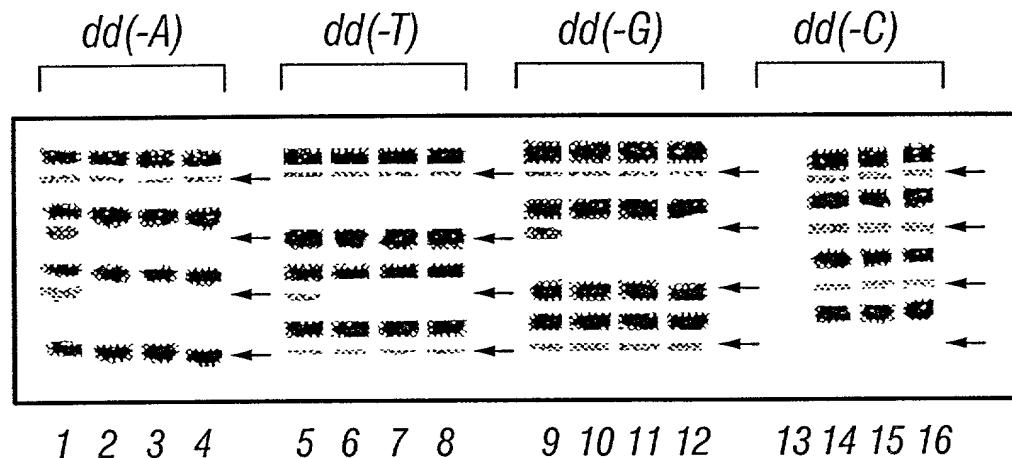


FIG. 25

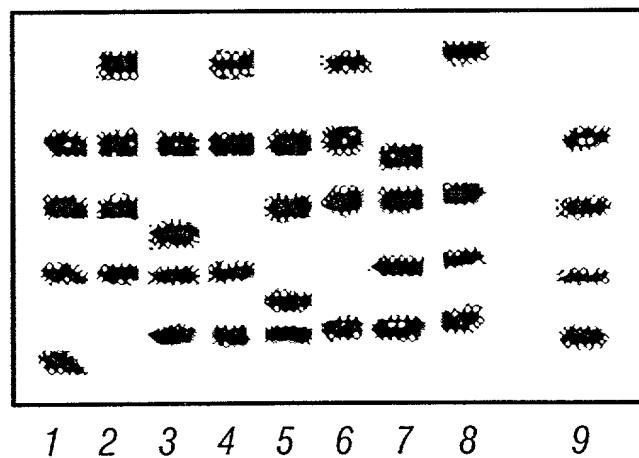


FIG. 26

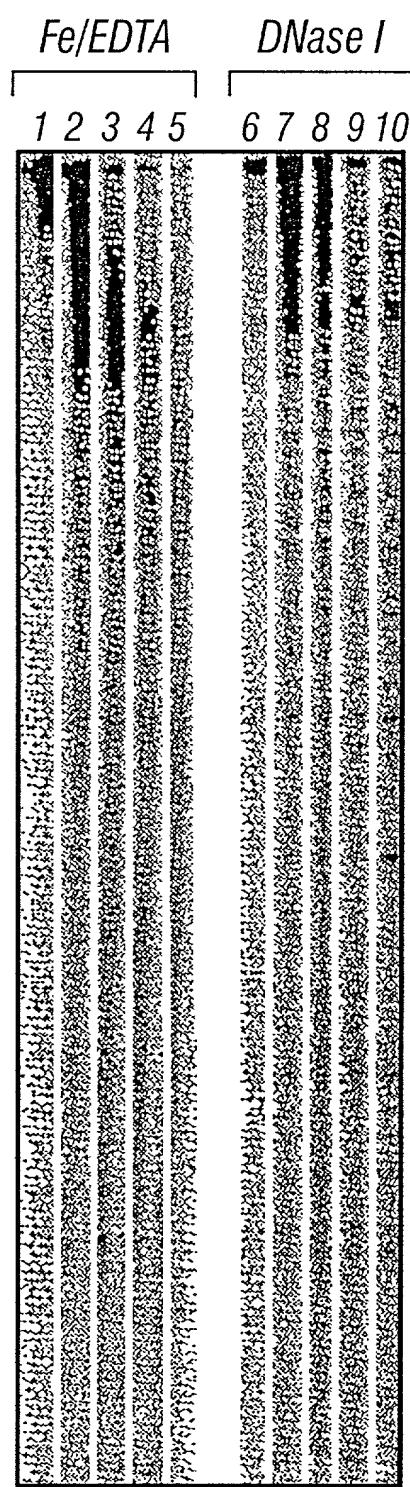


FIG. 27

EtBr staining

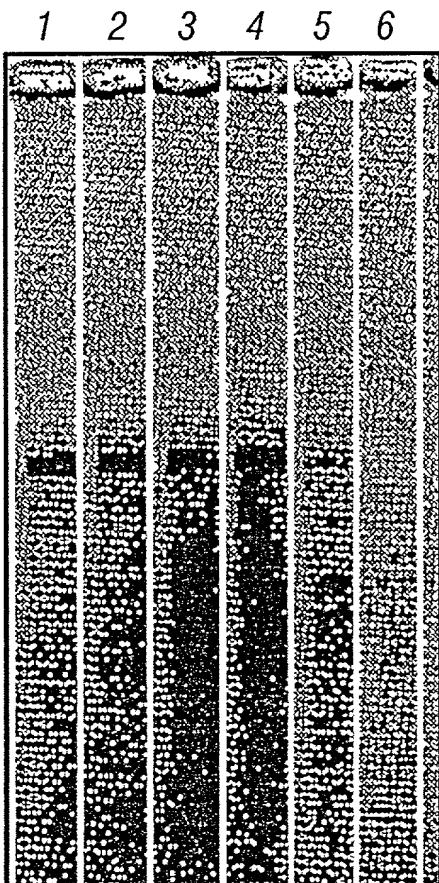


FIG. 28A

^{32}P -dATP

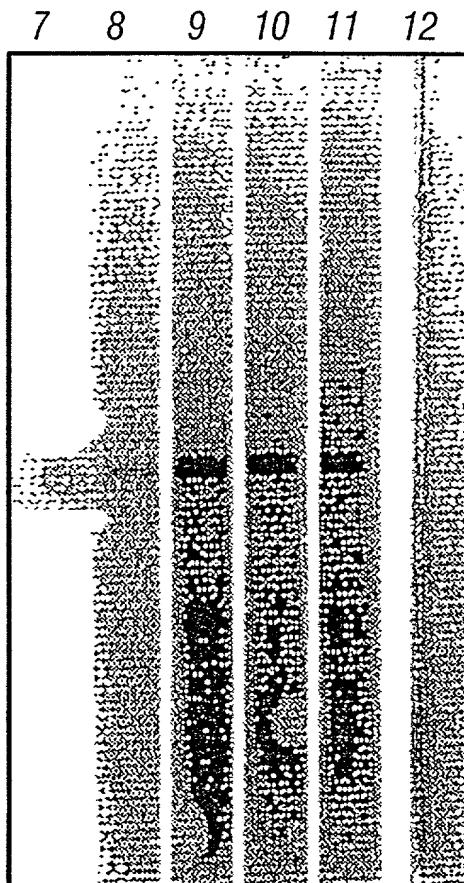


FIG. 28B

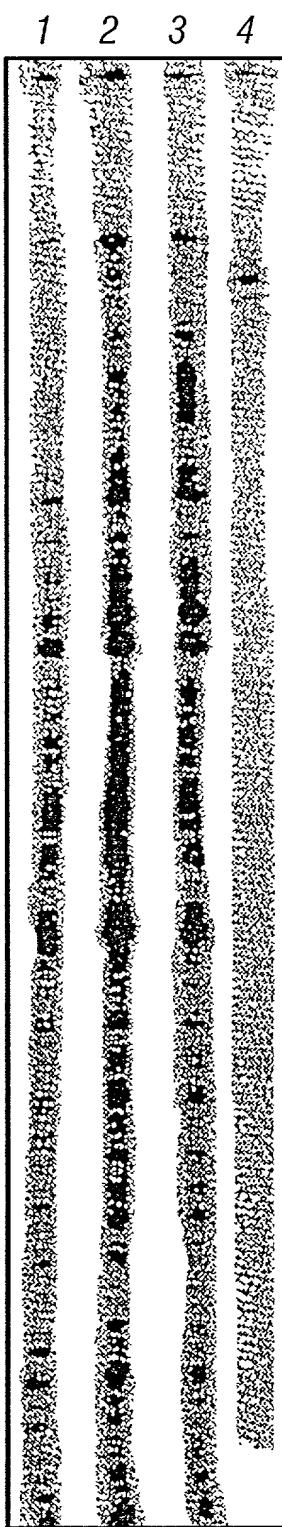
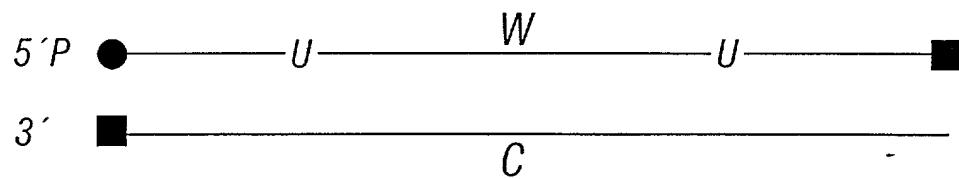


FIG. 29



- $5'$ -PHOSPHATE
 - $3'$ DIDEOXYNUCLEOTIDE OR NH_3 GROUP

FIG. 30A

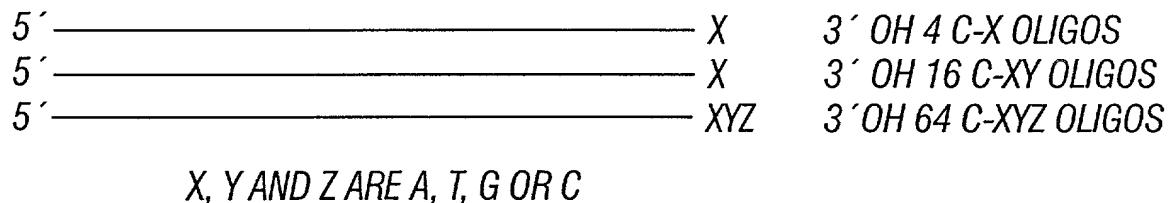


FIG. 30B

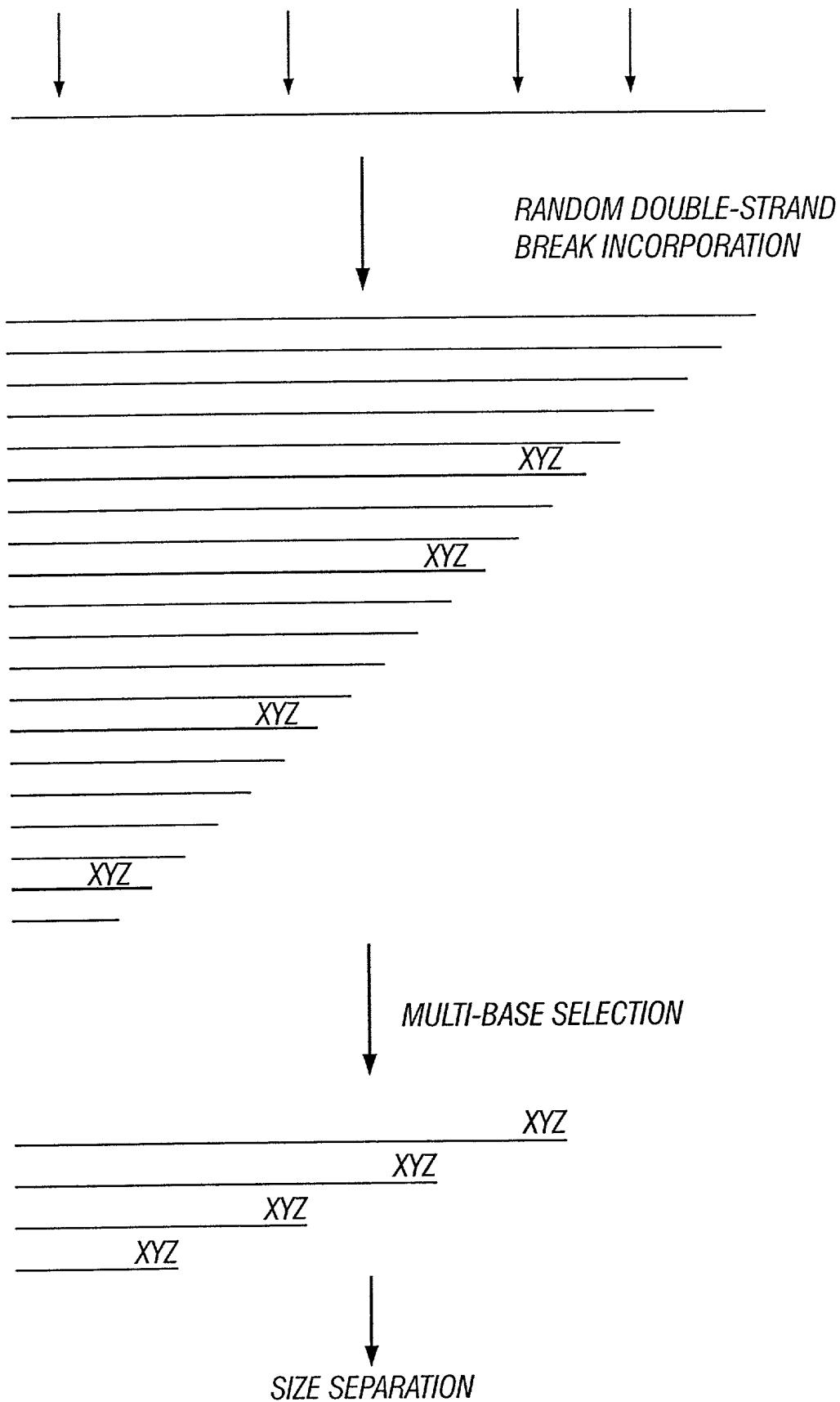


FIG. 31

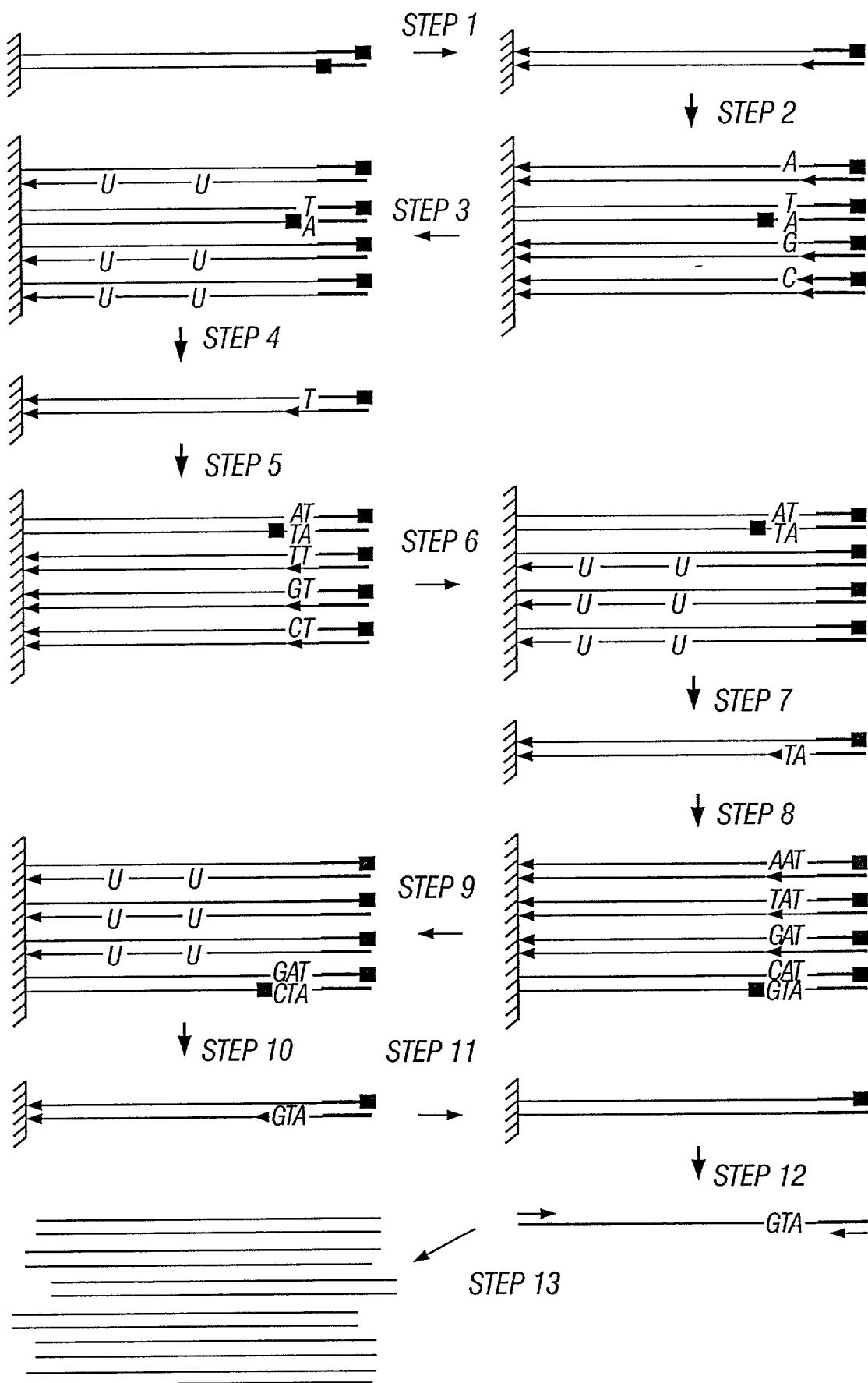


FIG. 32

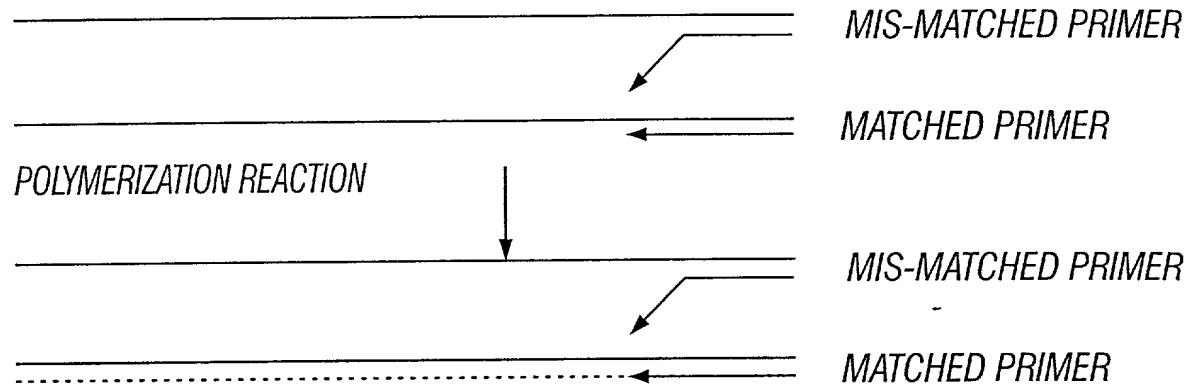


FIG. 33A

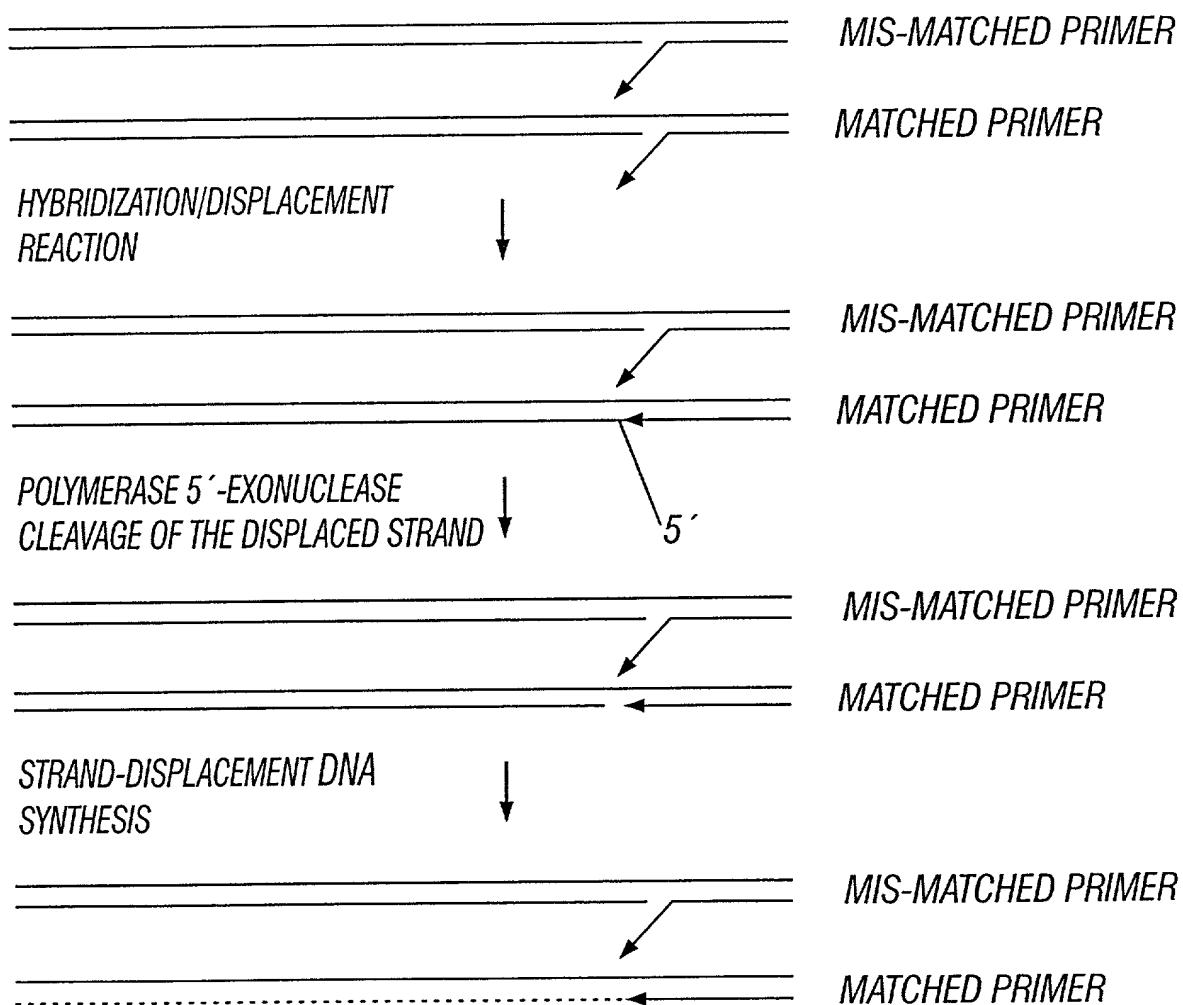


FIG. 33B